MRI DOWNSTAGING, PATHOLOGICAL RESPONSE AND MICROSATELLITE INSTABILITY STATUS IN PATIENT'S WITH SIGNET RING CELL CARCINOMA RECTUM UNDERGOING PREOPERATIVE LONG COURSE CHEMO IRRADIATION

DEPARTMENT OF RADIOTHERAPY
CHRISTIAN MEDICAL COLLEGE
VELLORE 632004

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF
MD BRANCH IX RADIOTHERAPY
EXAMINATION APRIL 2017

TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI- 600032.

CHRISTIAN MEDICAL COLLEGE, VELLORE

DEPARTMENT OF RADIOTHERAPY

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Dr. Thomas Samuel Ram

Professor

Department of Radiotherapy

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Dr Rajkrishna B

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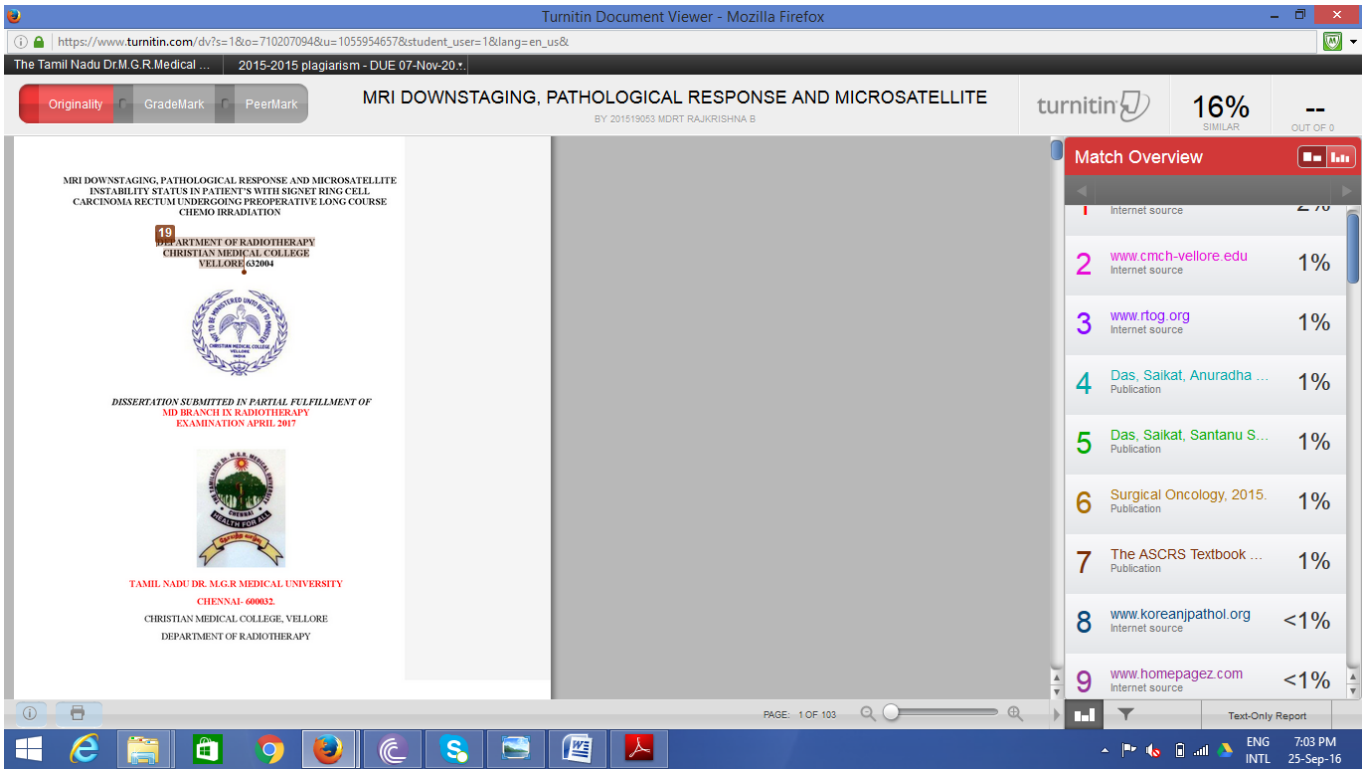
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19
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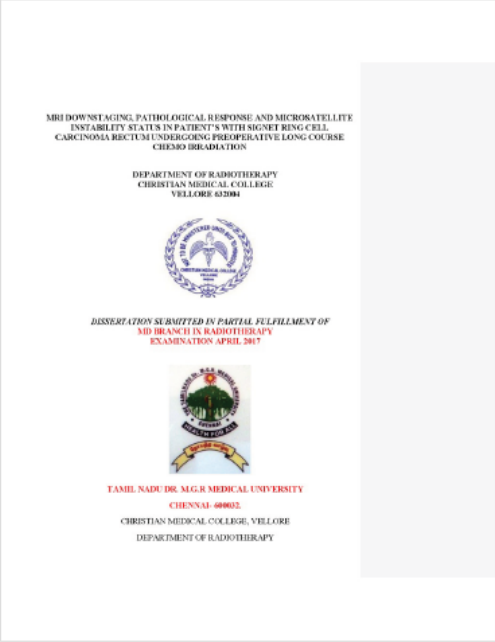

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Additional Vice-Principal (Research)

February 01, 2016

Dr. Rajkrishna B,
Department of Radiation therapy,
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MRI downstaging, pathological response and microsatellite instability status in patient's with signet ring cell carcinoma rectum undergoing preoperative long course chemoirradiation
Dr. Rajkrishna B, Employment Number: 21110 Department of Radiation therapy, Unit 1, Dr.Thomas Samuel Ram,, Employment number : 28155, Radiation Therapy Unit 1, Dr.Saikat Das (Employment number : 20423), Radiation Therapy Unit 2, Dr.Tharani Putta (Employment number :29040), Radiology, Dr.Rajat Raghunath (Employment number : 28850), Colorectal Surgery, Dr.Dipti Masih (Employment number : 32530), Pathology,

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The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "MRI downstaging, pathological response and microsatellite instability status in patient's with signet ring cell carcinoma rectum undergoing preoperative long course chemoirradiation" on December 03rd 2015.

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
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Institutional Review Board.

Dr. NIHAL THOMAS
MD, MNAMS, DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
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Cc: Dr.Thomas Samuel Ram, Dept. of Radiation therapy, CMC

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The Committee reviewed the following documents:

1. IRB Application format
2. Proforma
3. Information Sheet and Informed Consent Form (English, Hindi, Malayalam)
4. Cvs of Drs. Rajkrishna B, Thomas Samuel Ram, Saikat Das, Dipti Masih, Tharani Putta, Rajat Raghunath
5. No. of documents 1 - 4

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Name	Qualification	Designation	Affiliation
Dr. Nihal Thomas	MD, MNAMS, DNB(Endo), FRACP (Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), Deputy Chairperson(Research Chairperson), Member Secretary (Ethics Committee), IRB. CMC, Vellore	Internal, Clinician
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Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS, MCh	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Rajesh Kannangai	MD, PhD.	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. B. J. Prashantham	MA(Counseling Psychology), MA (Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Comm IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist

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Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgica Nursing, CMC, Vellore	Internal, Nurse
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "MRI downstaging, pathological response and microsatellite instability status in patient's with signet ring cell carcinoma rectum undergoing preoperative long course chemoirradiation" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in)

Fluid Grant Allocation:
A sum of 95,000/- INR (Rupees Ninety five thousand Only) will be granted for 2 years. 50,000/- INR (Rupees Fifty Thousand only) will be granted for 12 months as an 1st Installment. The rest of the 45,000/- INR (Rupees Forty five Thousand only) will be released at the end of the first year as 2 nd Installment.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
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Contents

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I extend my warm gratitude to my patients for participating in this study and spending their valuable time.

I would like to thank my parents and family members for their encouragement and support.

1. AIMS AND OBJECTIVES

AIM

To evaluate MRI down staging, pathological response and correlation of MSI status with Radiotherapy response in Signet Ring Cell Carcinoma Rectum.

OBJECTIVE

Primary Objective

MRI down staging and pathological response in Signet Ring Cell Carcinoma Rectum.

Secondary Objective

Correlation of microsatellite instability and Radiotherapy response in Signet Ring Cell Carcinoma Rectum.

2. INTRODUCTION

Worldwide, among the people diagnosed with cancer, colorectal cancer ranks third in males and second in females with 1.4 million new cases and 694,000 deaths in 2012, according to Global cancer statistics, 2012(2). Incidence rates are highest in Australia and New Zealand, Europe, and North America and the incidence rates are lowest in Africa and South-Central Asia(3).

In India according to National centre for disease informatics and research, rectal cancer ranks ninth among men and is uncommon among women(4) In rural areas , the incidence of rectal cancer is high(5).Incidence rates of rectal cancer varies from 5.5 to 1.6/100,000 among men and 2.8 to 0/100,000 among women. Unusually many young Indians are detected with rectal cancer(6).

Signet ring cell carcinoma rectum is one of the rare subtypes of rectal cancer. It accounts for about 1% of all subtypes of rectal cancers(86). It is predominantly seen in younger age groups , is locally advanced disease at presentation and carries poor prognosis(88) which is stage independent(86). They are also known to have high chances of distant metastasis (89).

In the evaluation of rectal cancer, magnetic resonance imaging plays a pivotal role. High resolution (HR) T2 weighted MRI of the pelvis helps in preoperative staging. It

helps in evaluating the extent of tumor, relationship to mesorectal fascia and involvement of circumferential resection margin (CRM).

Several randomized controlled trials have shown that neoadjuvant chemo irradiation followed by surgery gives significantly better outcome than surgery alone. Neoadjuvant radiation therapy helps in increased tumor down staging and decreased rates of local recurrence. While there is adequate literature on radiotherapy outcomes in rectal cancer, however specific data on neoadjuvant chemo irradiation outcomes in signet ring cell carcinoma rectum is not sufficient.

Microsatellites are tandemly repeated short DNA sequences throughout the genome. Microsatellite instability (MSI) will lead to impaired DNA mismatch repair. It occurs in 15% of all colorectal cancers. Preliminary studies suggest that impaired DNA mismatch repair genes correlates with increased sensitivity to radiotherapy.

Data on the response of signet ring cell carcinoma rectum to preoperative radiation therapy is very limited. There are few anecdotal reports of poor response of signet ring cell carcinoma of rectum to radiation therapy. MSI status in signet ring cell carcinoma of rectum may prove to be an important biomarker for radiation therapy response.

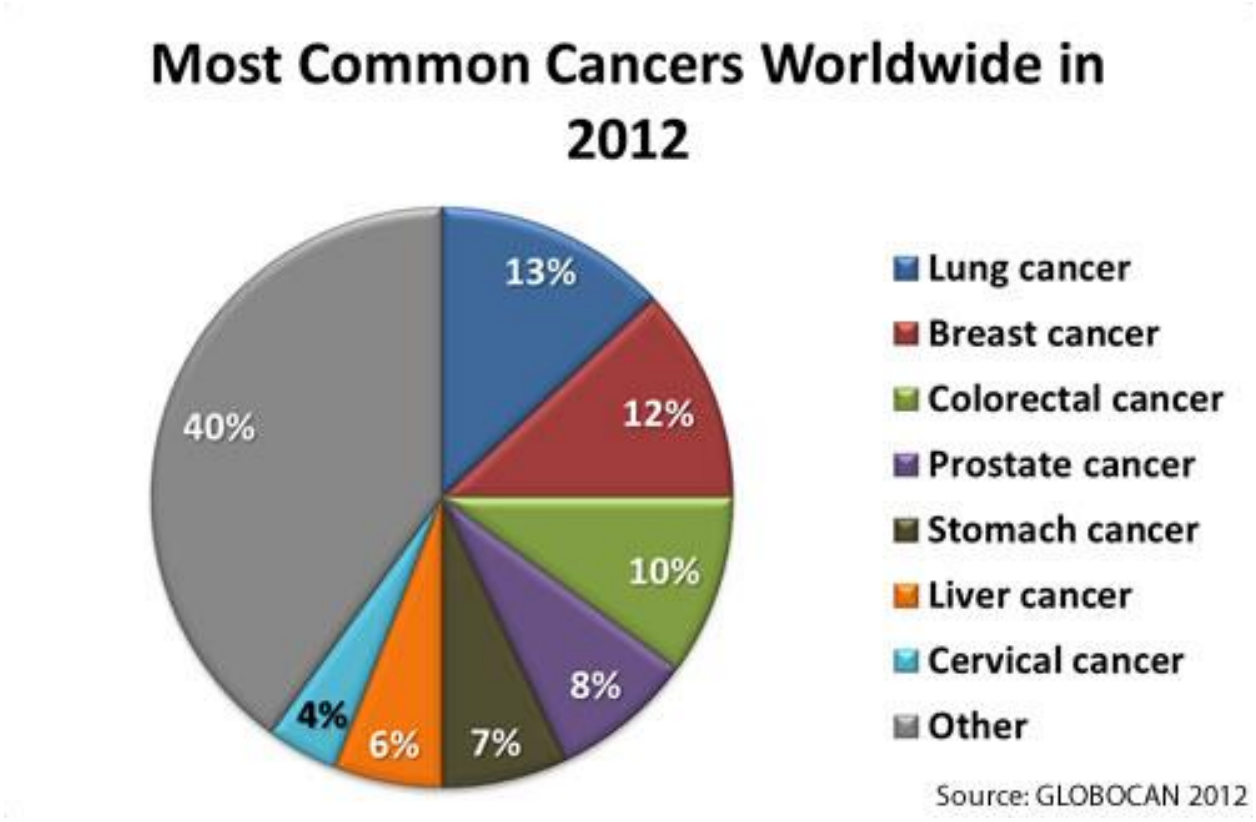
Hence in view of the paucity of data on radiological and pathological response to radiation therapy and MSI status in signet ring cell carcinoma of rectum we planned to undertake this study.

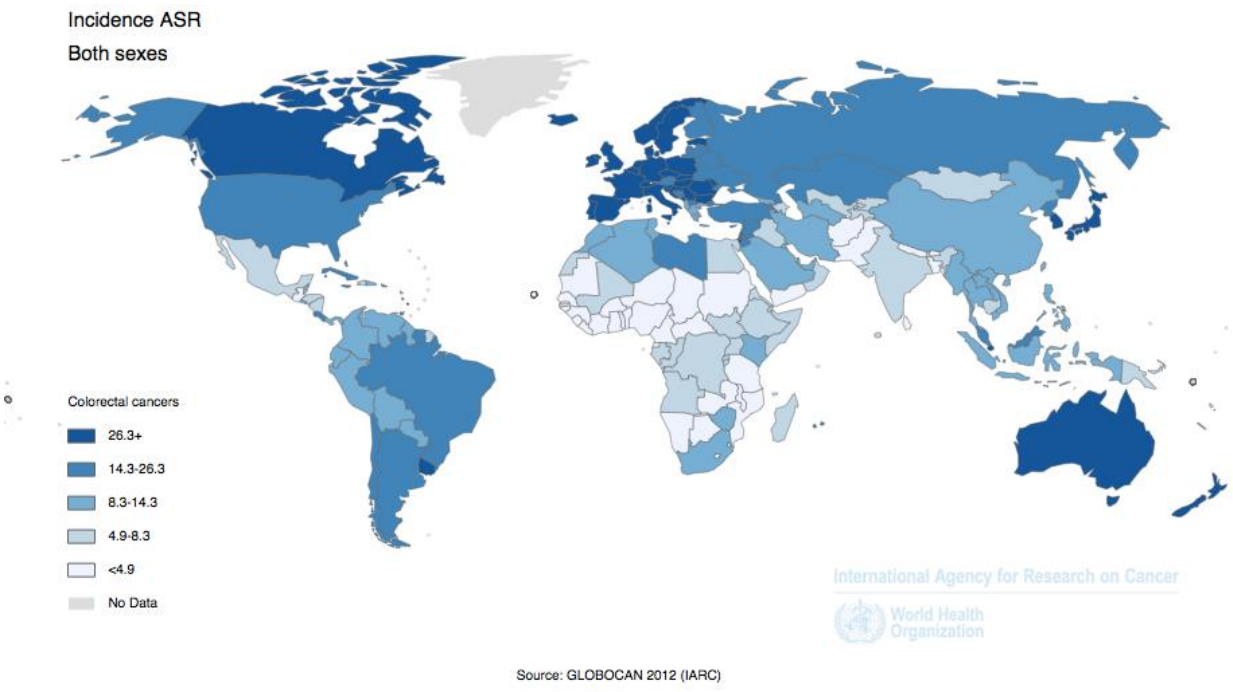
3. REVIEW OF LITERATURE

3.1 EPIDEMIOLOGY

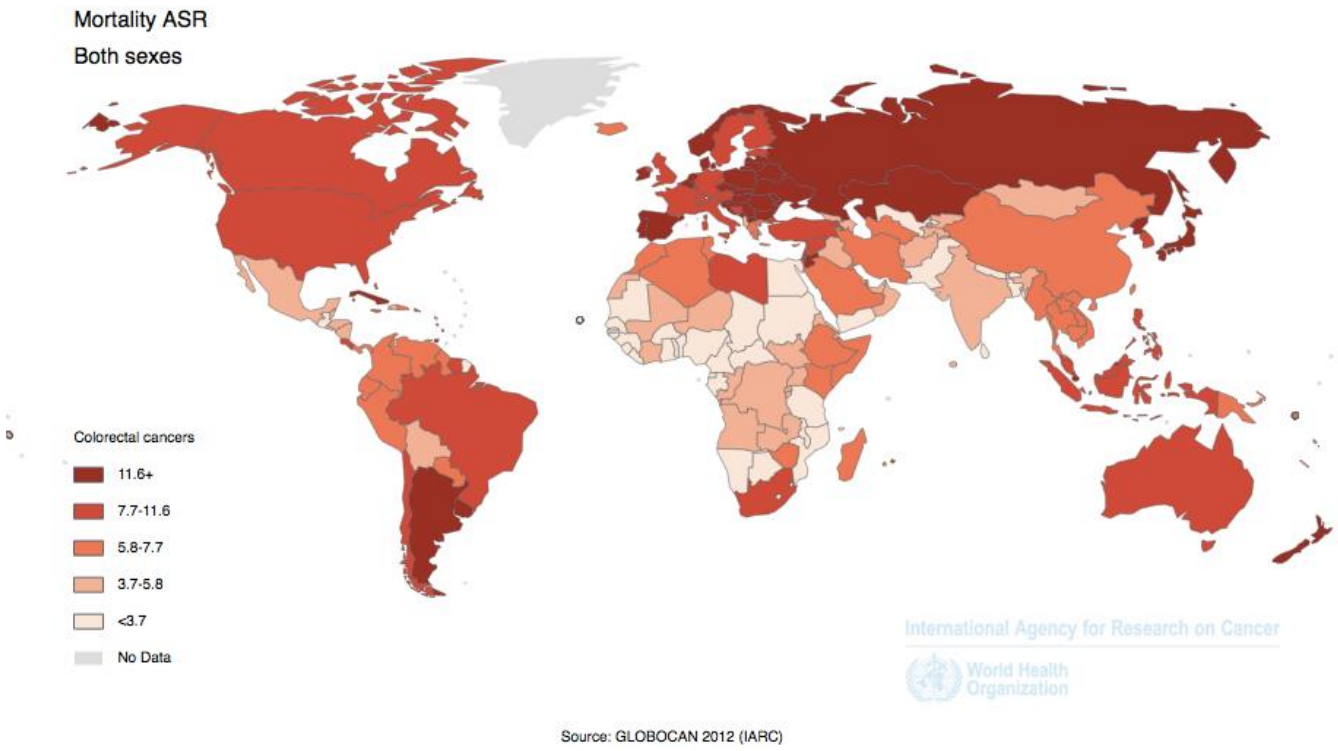
Worldwide, cancer is one of the leading causes of morbidity and mortality. There were approximately 14 million new cases and 8.2 million cancer related deaths in 2012. In men, most common sites of cancer in 2012 were lung, prostate, colorectum, stomach, and liver cancer and in women, most common sites were breast, colorectum, lung, cervix, and stomach cancer(1).

Worldwide, among the people diagnosed with cancer, colorectal cancer ranks third in males and second in females with 1.4 million new cases and 694,000 deaths in 2012(2). Incidence rates are highest in Australia and New Zealand, Europe, and North America and the incidence rates are lowest in Africa and South-Central Asia(3)





Worldwide incidence of colorectal cancers (ASR)

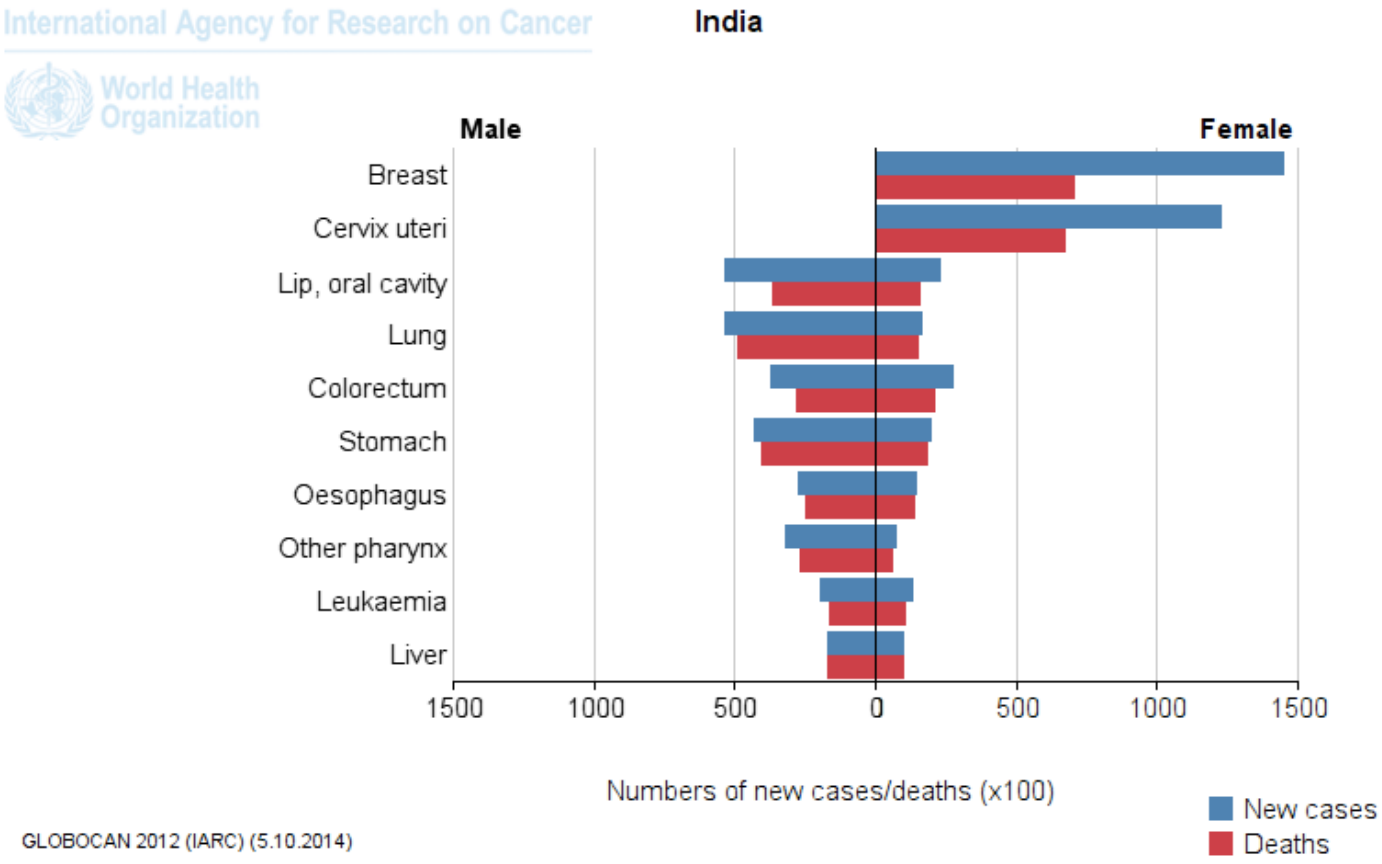


Worldwide mortality rates of colorectal cancers (ASR)

3.2 INDIAN SCENARIO

Incidence of colorectal cancer in India is relatively low as compared to the western world. Rectal cancer ranks ninth among men and does not include in top ten among women(4)In rural areas , the incidence of rectal cancer is high(5).Incidence rates of rectal cancer varies from 5.5 to 1.6/100,000 among men and 2.8 to 0/100,000 among women. Many young Indians were affected with rectal cancer(6). As the age increases, the risk of developing colorectal cancer increases. 90% are diagnosed at an age more

than 50 years with the average age of diagnosis is 64 years(7).One of the most important finding there has been increased number of younger (mean age of 40-45 years) patients from West Bengal, the North Eastern states and from Bangladesh with diagnosed colorectal cancer(8).



Ten leading cancers in the Indian population

3.3 RISK FACTORS

1. ***Age***: 90% occurs at 50 years or more. The chance of developing rectal cancer progressively increases after the age of 40,and sharply after the age of 50 (9).In our country some studies have shown that there has been an increase in young patients diagnosed with rectal cancer(3).
2. ***Adenomatous polyps*** : Neoplastic polyps are precursor lesions of colorectal cancers(10).An adenoma can change to malignancy in a long latency of about 10 years (11). Detection of and removal of these polyps before it become malignant can reduce the risk of invasive colorectal cancer(12).
3. ***Inflammatory bowel disease***: Ulcerative colitis and Crohn's disease both increase the risk of developing colorectal cancer later (10)
4. ***Family history of colorectal cancer or adenomatous polyps***: Increased high risk among first-degree family members of patients diagnosed with colorectal cancer and adenomatous polyps. About 20-25% of colorectal cancers are found among the first-degree family members(13,14).
5. ***Genetic syndromes***: 5 to 10% of colorectal malignancies are associated with genetic syndromes, such as FAP, Gardner, Lynch and Turcot.
6. Major other risk factors include physical inactivity, obesity, diet less in fruits and vegetables and smoking(15). Obesity can increase the risk of colorectal cancer by

19%. Role of lifestyle in the development of colorectal cancer remains an area of research. Fish consumption can lead to reduced risk of colorectal cancers and is is due to omega 3 and omega 6 polyunsaturated fatty acids(16).

One study showed there was no significant risk for chewers, smokers and alcohol drinkers for developing colorectal cancers when compared to those without the habits. Cabbage eaters had 50% reduction in risk. Fresh fish eaters had a 40–70% reduction in risk. Dark-green-leafy-vegetables did not have protective effect on development of colorectal cancers. Some nondietary risk factors are genetic predisposition, tobacco smoking and ulcerative colitis(17)

3.4 ANATOMY

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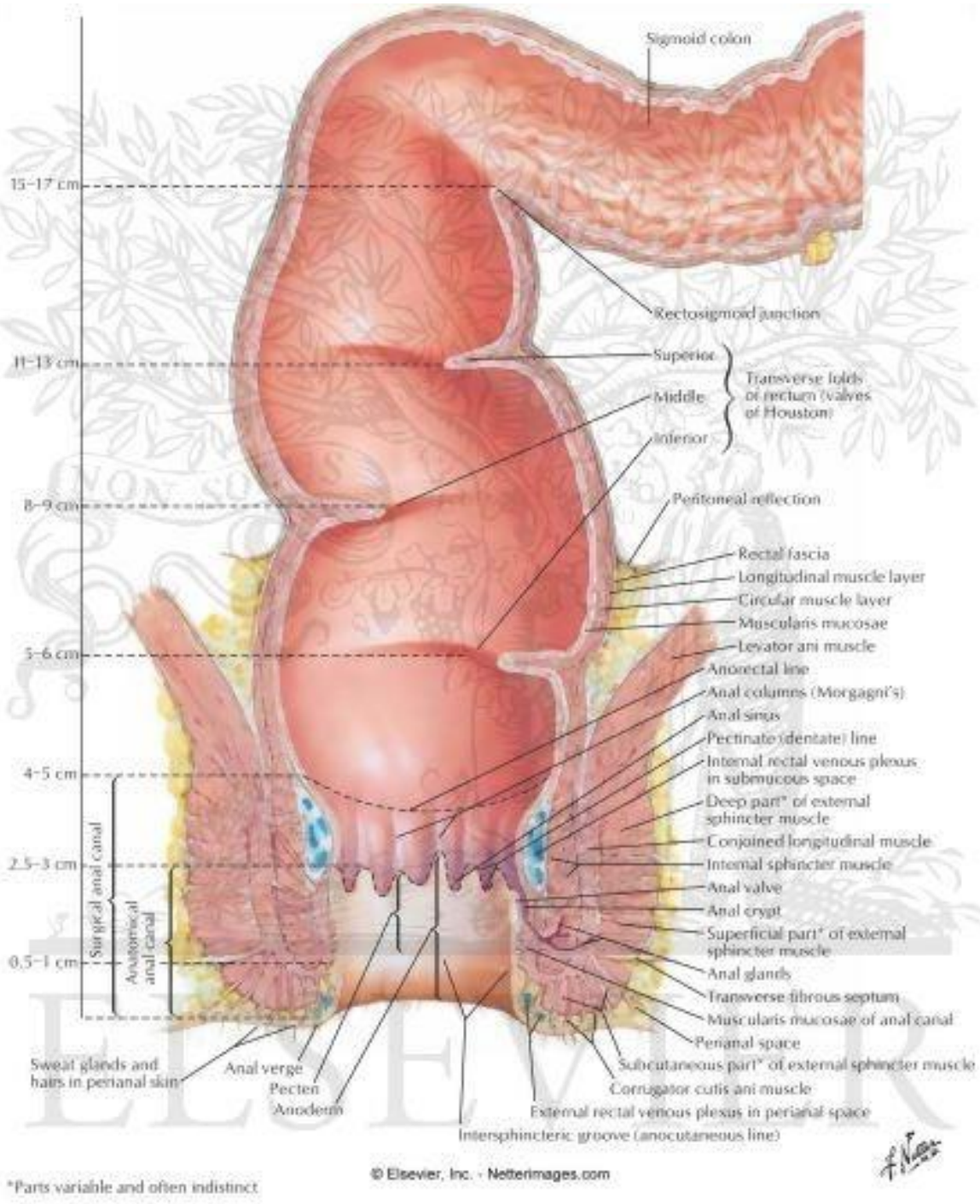
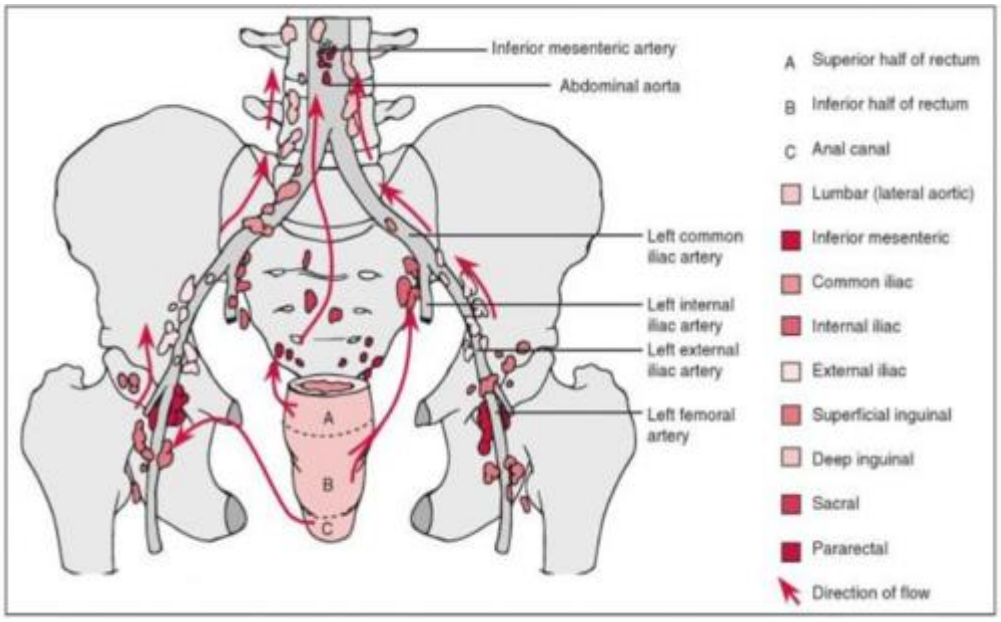
The terminal portion of large intestine is rectum. It extends from recto sigmoid junction to approximately 12 to 15 cm and ends at the level of the levator ani. The blood supply of the rectum comes mainly from the superior hemorrhoidal artery and supplies the proximal two-thirds of the rectum. The middle hemorrhoidal artery supplies the lower one-third of the rectum. Superior rectal vein drains into inferior mesenteric vein and from there into the portal circulation. Middle rectal vein drains to the internal iliac vein and thereafter into inferior vena cava(18).

SURGICAL ANATOMY OF RECTUM

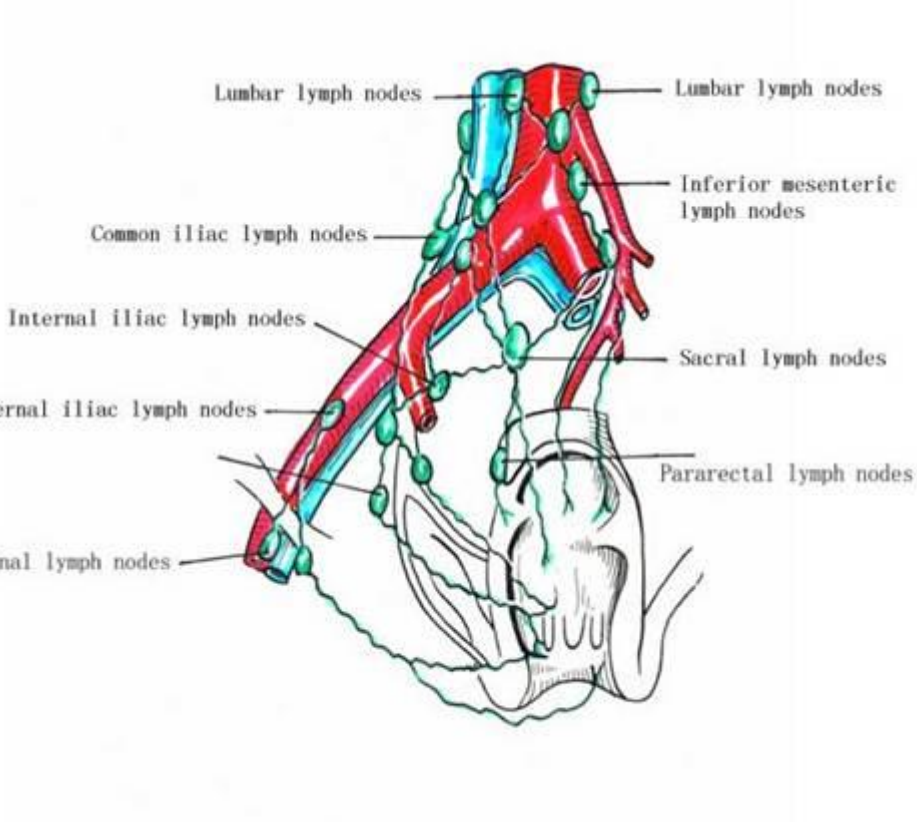


*Parts variable and often indistinct

Lymphatic drainage of upper two-thirds of the rectum is to inferior mesenteric nodes and then to para-aortic nodes. Lower one-third of rectum drains superiorly along the superior hemorrhoidal artery and laterally along the middle hemorrhoidal artery to nodal basin along the internal iliac artery(19).



LYMPHATIC DRAINAGE OF RECTUM



Rectum is divided into upper one third (12–16 cm), middle one third(6–12cm),and lower third (within 6 cm) from the anal verge(20).

Investing fascia propria envelopes the rectum, perirectal fat and plexus of blood vessels. The tissues surrounding the rectum bound by the fascia propria is called as the mesorectum. The mesorectum contains perirectal lymph nodes(18).

The location of the tumor is usually specified in terms of the distance from the anal verge. The reference anatomical landmark from which the measurements are made, have to be clearly mentioned. Likewise, the method of measurement; per rectal

examination, colonoscopy, flexible endoscopy has to be mentioned. The location of the tumor is important in the prognosis and selection of appropriate therapy

The upper third of the rectum is bordered by visceral peritoneum known as the anterior peritoneal reflection. The middle third is covered by the peritoneum anteriorly. The lower third of the rectum is extra peritoneal and is bounded by Denonvilliers fascia. . Posteriorly, the presacral fascia is continuous with the posterior part of the mesorectal fascia or Waldeneyer fascia(21).

3.5 DIAGNOSTIC EVALUATION

It includes a detailed history, clinical examination including a per rectal examination, complete blood cell counts, liver function tests, renal function test and a baseline CEA. Colonoscopy or barium enema to look for polyps in the large intestine and synchronous growths. Imaging studies include a CT or MRI of the abdomen and pelvis for accurate extent of the tumor and to rule out metastasis in other abdominal organs. PET CT is done in some cases to help in exclusion of distant metastasis. It is more useful in cases of a recurrent or a suspected recurrent growth (22).Endorectal Ultrasound is being the imaging modality of choice for accurate T staging of the growth (23). A chest radiograph or a CT thorax is done to rule out lung metastasis.

A biopsy of the growth is the most important for confirmation of histology and is done at the time of the Colonoscopy / sigmoidoscopy or as a guided procedure using endorectal ultrasound or CT scan.

The staging of patients with rectal cancer is carried out based on the TNM staging based on the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging systems.

STAGING (TNM) AJCC SEVENTH EDITION (24)

Primary tumour staging (T)

Tx : primary tumour cannot be assessed

T0 : no evidence of primary tumour

Tis : carcinoma in situ

T1 : submucosal invasion

T2 : muscularispropria invasion

T3 : subserosal invasion or into non peritonealised perirectal tissues

T3a : extends <1 mm beyond muscularis propria

T3b : extends 1-5 mm beyond muscularis propria

T3c : extends 5-15 mm beyond muscularis propria

T3d : extends 15 mm beyond muscularis propria

T4 : invasion into other organs or structures and/or perforates visceral peritoneum

T4a : tumour penetrates to visceral peritoneum

T4b : invades to other organs or structures

Regional lymph nodes (N)

Nx: regional nodes not assessed

N0: no regional lymph nodes

N1: metastasis in 1-3 regional (perirectal) lymph nodes

N1a: metastasis in one regional lymph node

N1b: metastasis in 2-3 regional lymph nodes

N1c: tumor deposit(s) in the subserosa, mesentery, or non peritonealized pericolic or perirectal tissues without regional nodal metastasis

N2: metastasis in 4 or more regional lymph nodes

N2a: metastasis in 4-6 regional lymph nodes

N2b: metastasis in 7 or more regional lymph nodes

Metastases **(M)**

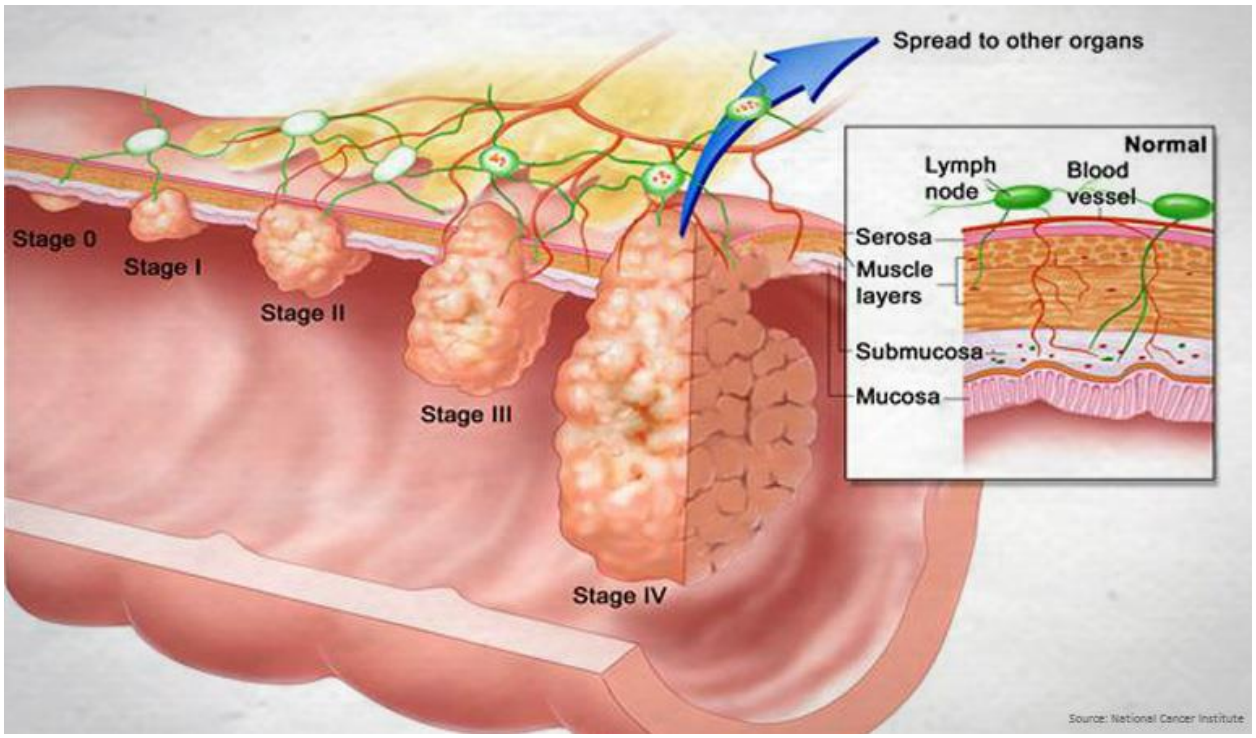
Mx: cannot be assessed

M0: no distant metastasis

M1: distant metastasis

M1a: metastasis confined to one organ or site

M1b: metastases in more than one organ/site or the peritoneum



3.6 MANAGEMENT OF RECTAL CANCER

Management of rectal cancer involves multidisciplinary approach. During 1980s surgery was the only treatment for rectal cancer and there were more than 50% local recurrence after surgery. Many trials have found out that post operative radiation therapy decreases the local recurrence and introduction of 5 fluorouracil as adjuvant chemotherapy decreased the distant metastasis(25,26). In 1990s , with introduction of total mesorectal excision(TME) and neoadjuvant radiation therapy, further better local control was

achieved.TME has revolutionized the outcomes in resectable rectal cancer leading to significant lower local recurrence rates at 10-year follow-up(27–29).

German Rectal Cancer trial proved that the local recurrence rates were lower in pre-operative chemo irradiation group than in the post-operative chemo irradiation group(p=0.006) and thus neoadjuvant chemo irradiation became the standard of care(30).Neoadjuvant chemo irradiation has helped in effective down staging the tumor and 15 to 25% pathological complete response (p CR)(31).

3.7 ROLE OF MRI IN RECTAL CANCER

In the evaluation of rectal cancer, magnetic resonance imaging plays a pivotal role. High resolution MRI helps in preoperative staging. It helps in evaluating the extent of tumor, relationship to mesorectal fascia and involvement of circumferential resection margin (CRM). MERCURY trial assessed the accuracy of MRI to predict resection with curative intent and found out 92% specificity to predict negative circumferential margin (CRM) (32). Follow up results after 5 years of the same study showed that CRM clear preoperative MRI was significant for overall survival , disease free survival and local recurrence. MRI involvement of the CRM was significantly associated with distant metastases(33).

Good prognostic group identified by MERCURY trial has following features(34)

1. CRM not involved
2. Extramural invasion not present
3. T2 or T3a or T3b
4. < 5mm spread from the muscularis propria
5. intersphincteric plane is not involved

Following neoadjuvant chemo irradiation, MRI pelvis is done to see the tumor regression grade and CRM and helps to refine treatment plans according to the response. Studies have shown that ,after preoperative chemo irradiation ,MRI showed down staging by achieving both tumor and lymph node down staging(35) . Thus post neoadjuvant chemo irradiation MRI can assess tumor response before surgery. But its role in predicting survival outcomes has not been studied. This can be achieved by applying principles of histopathology evaluation and low signal intensity appearance of fibrosis in MRI(36). Mandard tumor response grading system to assess TRG(37).

Tumor response was graded as follows:

TRG 1 - complete regression with absence of residual cancer and fibrosis extending through the wall (complete response)

TRG 2 – rare residual tumor cells scattered throughout the fibrosis (near complete response)

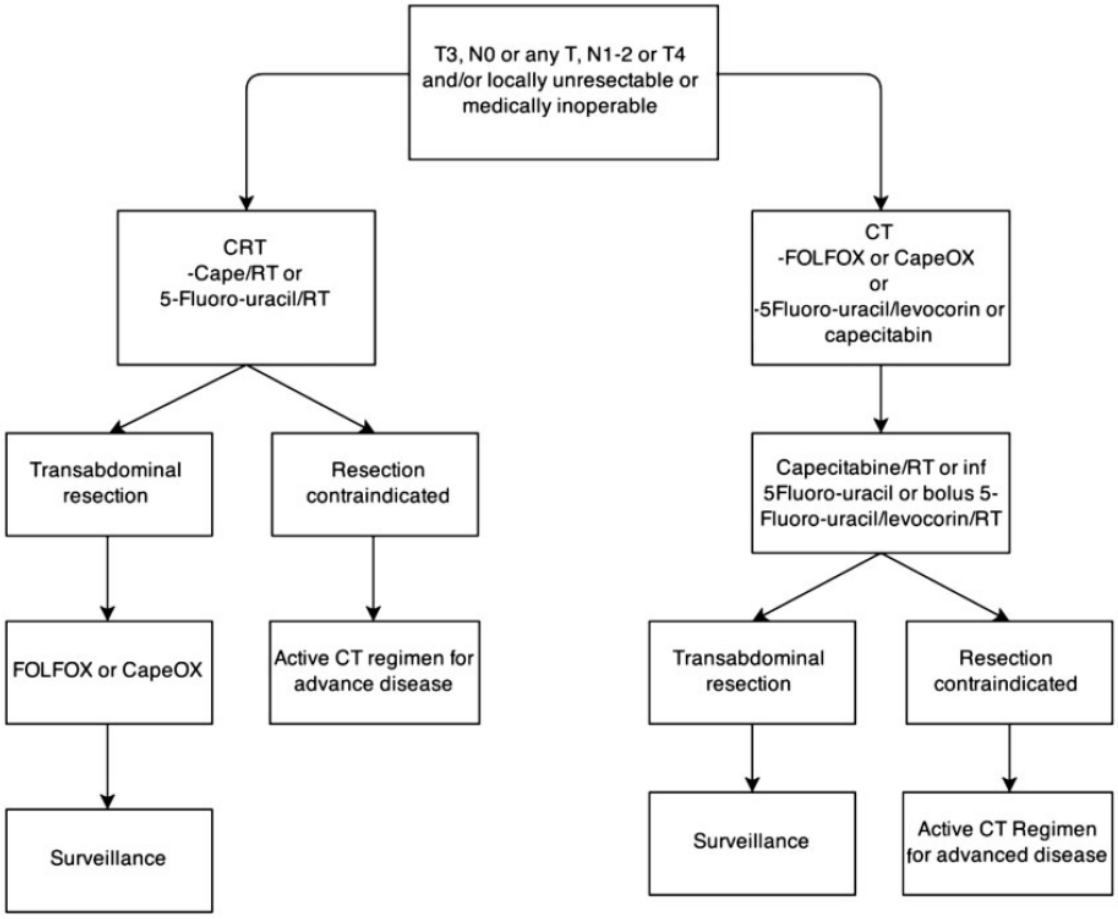
TRG 3 - predominant fibrosis but increase in the number of cancer cells (moderate response)

TRG 4 - residual cancer cells outgrowing the fibrosis (minimal response)

TRG 5 - absence of regressive changes (no response).

Sathyakumar etal has shown that visual assessment complete response on post chemo irradiation diffusion weighted MRI is an important predictor of complete response(122)

Based on NCCN guidelines, rectal cancer with stages T3N0 or any T with N1 or N2, the standard of care is long-course chemo irradiation, followed by TME and then adjuvant chemotherapy(38)

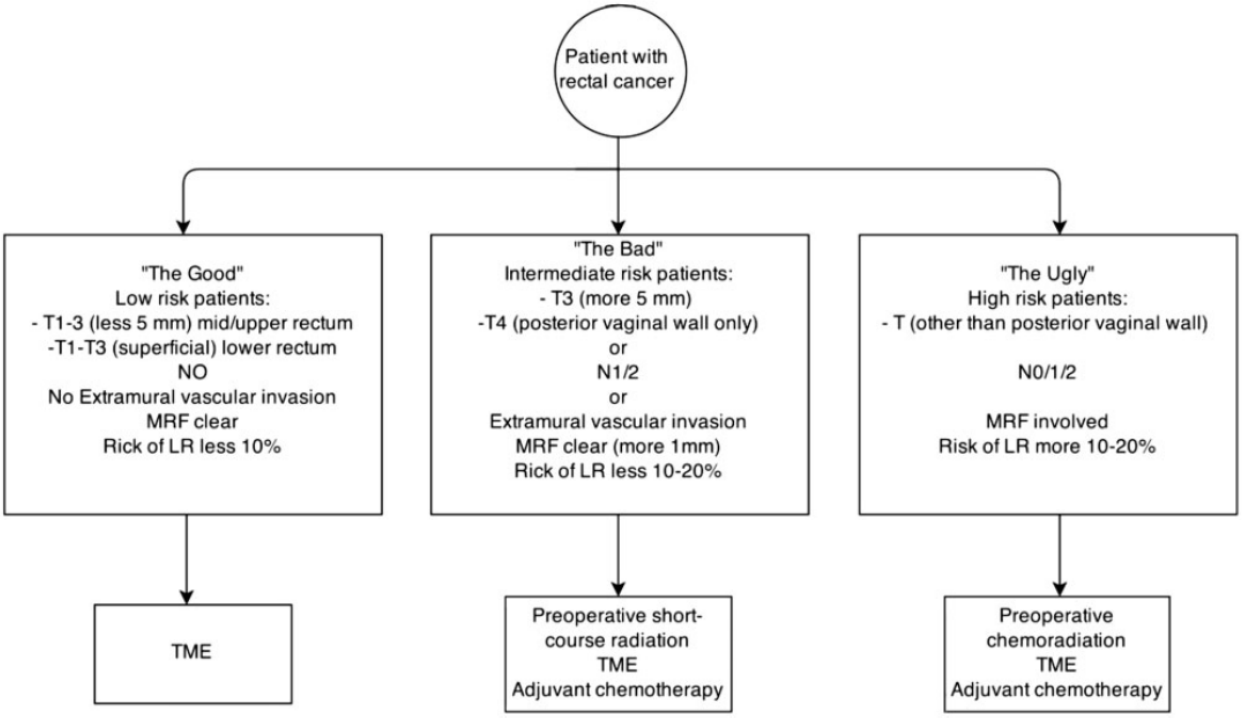


In Europe and Scandinavia, depending upon MRI findings patients are divided based on risk(39,40)

1) low risk (“the good”)

2) intermediate risk (“the bad”)

3) High risk (“the ugly”).



3.8 SHORT COURSE RADIOTHERAPY AND LONG COURSE CHEMOIRRADIATION

Local control and low-recurrence rates can be obtained by pre-operative short course radiation therapy (SCRT total dose of 25 Gy in five fractions) or long-course chemo irradiation (LCCRT) (50.4 Gy in 28 fractions) with concurrent chemotherapy with 5 fluoropyrimidine followed by surgery. No concurrent chemotherapy is given with short course radiation and surgery is done within 7 days. After long course chemo irradiation the surgery is done after 6 weeks to 8 weeks(30,41,42)

Two randomized trials compared SCRT and LCCRT.

Polish trial took T3–T4 lesions and seen the difference in sphincter preservation rates and found that proportion of sphincter preservation surgery was similar. It also showed down staging and complete response were more in patients who received LCCRT. Local control and survival were not significant(41).

Trans-Tasman Radiation Oncology Group took T3N0-2M0 tumors and within 12cm from anal verge. They randomized to SCRT or LCCRT followed by surgery after 4–6 weeks followed by adjuvant chemotherapy for 4 weeks. SCRT group had high local recurrence, but statistically not significant. Pathological complete response was more with LCCRT(42),

NSABP R04 study showed that 5-fluoro uracil (5-FU) or capecitabine have equal effects. But adding concurrent Oxaliplatin and 5 FU with radiation had no increased benefits(43). ACCORD study also showed adding concurrent Oxaliplatin and 5 FU with radiation had increased toxicity(44)

Targeted therapies have been used in rectal cancer. This includes VEGF inhibitor Bevacizumab and EGFR inhibitors, cetuximab and panitumumab.From phase I and II studies, it is not clear that addition of cetuximab to chemo irradiation will result in down staging. Phase I and II trials showed that bevacizumab can be safely combined with neoadjuvant chemo irradiation. It can lead to cell killing by damaging tumor blood

vessels and can normalize tumor vascularity and results in increased tumor oxygenation and thus causing in increased radio sensitivity(45)

Management of patient's who had complete response after LCCRT is controversial. Some studies did wait and watch policy without immediate surgery. The first reports showed a 5-year disease-free survival rate of 95% and an overall survival rate of 100% in the case of a clinical complete remission. But only 25% to 50% of the patients achieving a clinically complete response will have a true pathological complete response (46)

3.9 SURGERY IN RECTAL CANCER

Surgery is one of the main stay treatments in rectal cancer.

3.9.1 LOCAL EXCISION

1. **Trans anal approach**

This option can be used for tumors that are less than 8cm from the anal verge. Proximal tumors cannot be approached using this technique.

2. **Trans-Sphincteric (York Mason) approach**

The entire anal sphincter is divided in the midline. Used for tumors near the anorectal region.

3. **Posterior para sacral (Kraske) approach**

It is used for proximal growth. Para sacral longitudinal excision from the just above the anus to the inferior aspect of the gluteus maximus.

The entire growth has to be removed in one uninterrupted specimen, so that the Pathologist is able to give a better description of the margin. The above mentioned techniques do not help in lymph nodal sampling. Studies have shown that the incidence of lymph nodal metastasis in T1 lesion is 5-10%.But in T2 lesions it is 20-35%(47). This high rate of lymph nodal metastasis makes local excision unsuitable for T2 lesions.
Local excision is only done for small tumors which are less than 4cm, clinically T1 or favorable T2 and are about 8-10 cm from anal verge. They are usually well to moderately differentiated mobile lesions that occupy less than 40% of the circumference.

At present, local excision is recommended for small growths that are usually less than four centimeters, less than 8-10 cm from anal verge, clinically T1 or occasionally, favorable T2 lesions. They are usually well to moderately differentiated mobile lesions that occupy less than 40% of the circumference(48,49).

Other locally advanced rectal tumors need different surgical options.

3.9.2 LOW ANTERIOR RESECTION

Low anterior resection (LAR) helps in sphincter sparing surgery without compromising local and distant control(50). LAR is done for upper third, middle third and in some

lower third tumors(51).The advantage of the LAR is the possibility to spare the sphincter and this will result in better quality of life as they do not require colostomy and also less post operative complications of poor sphincter control, bowel urgency and frequency(52).

3.9.3 ABDOMINOPERINEAL RESECTION

Abdominoperineal resection (APR) is the gold standard surgery for distal rectal tumors. It requires a proctectomy and permanent colostomy. The anatomy of the pelvis, the proximity to the prostate or the vagina and the thin mesorectum has a considerable bearing of the margins achieved following surgery(53).APR is a morbid surgery than LAR. Patients have a poor quality of life due to permanent colostomy(54).

3.9.4 TOTAL MESORECTAL EXCISION

Local recurrence rate were 15-30% after LAR or APR. This high rate of local recurrence can be attributed to lateral spread to tumor is not only seen at the level of tumor but also all through the mesorectum. Total mesorectal excision (TME) is the sharp dissection along the plane to separate the visceral and the parietal layers of the endopelvic fascia. The entire rectal growth and the entire mesorectum is dissected out in one uninterrupted specimen(55). This surgery helps to get better margin and thus resulting in better local and distant control(56). Minimum of 12-15 nodes has to be dissected for complete pathological staging(57). TME has slightly high rates of complications like anastomotic

leak and delayed wound healing. It has higher rates of local control. Both open and laparoscopic TME has similar oncological outcomes(58).

Recent surgical advances include extra levator APR, laparoscopic approaches for TME, ultra low LAR and robotic LAR and TME. The major disadvantage is these techniques are available only in few centres and the associated cost and lack of expertise(56).

3.10 ADJUVANT THERAPY IN RECTAL CANCER

Local failure rates were high after surgery alone, 25-30%(59). Adjuvant therapy is needed for local and distant control.

Adjuvant Radiotherapy alone

Large radiotherapy portals are needed in post operative radiotherapy. Moreover , regardless of the surgical techniques the main concern was the large small bowel volumes and hypoxic tumor bed. Studies comparing surgery alone versus surgery followed by radiotherapy has shown better local control, but had no disease free or overall survival benefit(59,60).

Adjuvant chemotherapy

Adjuvant chemotherapy alone had shown higher local failure rates, 10-15%(60).

Adjuvant chemo irradiation

With the use of adjuvant chemo irradiation there was increase in disease free and overall survival. However there were increased toxicity when compared to adjuvant chemotherapy or adjuvant radiotherapy alone(61,62).

Adjuvant chemo irradiation versus adjuvant radiotherapy

Adjuvant chemo irradiation has shown better local control and overall survival and significant decrease in distant metastasis rate(62).

Neoadjuvant radiotherapy

Neoadjuvant therapy helps in down staging the tumor and helps in better resection with adequate margins. It may also help in sphincter sparing approach. Preoperative radiotherapy helps in better local control and overall survival. Early trials used short course radiation therapy followed by surgery after a short interval(63). Another study which addressed the interval between completion of radiotherapy and surgery has shown that longer duration helps in significant down staging and significant pathological response rate(64).There has been higher rates of complications with preoperative radiotherapy like bowel urgency, incontinence and faecal soiling. Preoperative radiotherapy followed by TME when compared to TME alone had showed a lower local relapse in the pre operative radiotherapy patients(65).Metaanalysis showed preoperative radiotherapy was associated with lesser local relapse and better overall survival(59).

Preoperative chemo radiotherapy versus preoperative radiotherapy

Studies have shown that preoperative chemo irradiation has resulted in higher pathological response rate and lower local relapse rate. But toxicity profile was higher. There was no overall survival benefit(44,66).

In a study , after a median follow up of 11 years, it has shown a benefit towards local control in preoperative chemo radiotherapy arm. There was no improvement in over all survival(30). EORTC trial also showed similar results(66,67).

Neoadjuvant Long Course chemo radiation (LCCRT) followed by surgery is the standard of care for all locally advanced rectal cancers.

Preoperative short course radiotherapy versus long course neoadjuvant chemo radiotherapy

A trial had compared these two and has shown that there was higher rate of down staging and good pathological response following long course chemo radiotherapy. There was no significant difference in toxicity, overall survival and local recurrence rate(42).

Preoperative versus post operative therapy

Studies have shown that there was benefit with preoperative chemo radiotherapy in reducing the pelvic recurrence, increasing down staging and increase in the number of sphincter sparing surgeries. There was no benefit in disease free survival and overall survival. There was less acute toxicity with preoperative chemo radiotherapy arm(30).

There was another trial to evaluate pre operative short course radiotherapy versus post operative chemo radiotherapy. Pre operative arm had lesser number of local recurrences. Increased disease free survival was seen at 3 years. But there was no significant increase in the overall survival(68).

ROLE OF CAPECITABINE

Capecitabine is an oral fluoro pyrimidine. Thymidine phosphorylase converts Capecitabine into the active drug (5-FU) within tumors cells. The studies comparing infusional 5-FU versus Capecitabine showed the equal benefit regarding disease free and overall survival. The toxicity profiles were slightly different. Capecitabine had hand foot skin reactions and proctitis, whereas the patients on infusional 5-FU had myelosuppression (69)

3.11 PROGNOSTIC FACTORS IN RECTAL CANCER

Location : Distal tumors have worst prognosis than proximal tumors(70,71)

Studies have shown that, for pT3a the cancer-related 5-year survival rates was 85.4% and for pT3b it is 54.1%. So the identification of high risk patients with an extramural tumor spread of 5-mm depth .of extramural tumor invasion directs the treatment.(72).

The depth of spread beyond the muscularis propria had increased risk of involvement of lymph node metastasis(73). Lymph node positivity is an independent worse prognostic factor and is more when 4 or more lymph nodes are involved(74).

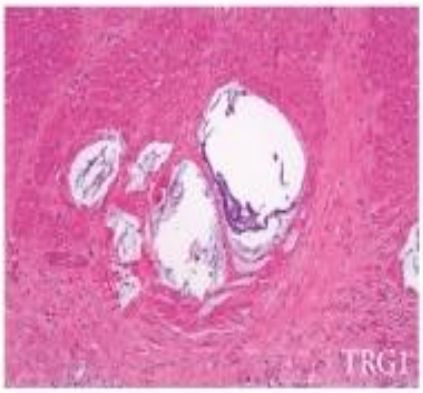
Positive circumferential resection margin (CRM) is a poor prognostic factor. CRM involvement is an indicator of advanced disease than inadequate local surgery. 40% of patients prone to develop distant metastases(75).

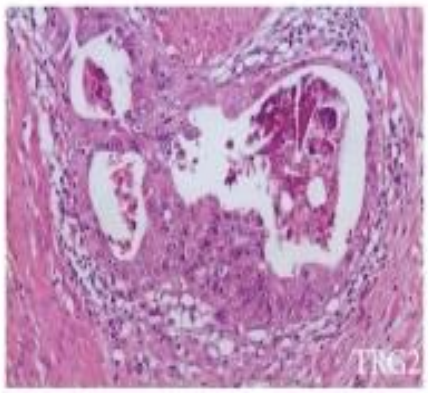
Histology such as signet ring cell type or melanomas have a poorer prognosis(76). Poorly differentiated tumors are associated with poor prognosis. Lymph vascular invasion is an independent factor for poorer prognosis(77,78)

Fixed tumors have poor surgical outcomes and this in turn translates into poor local control and survival(79,80)

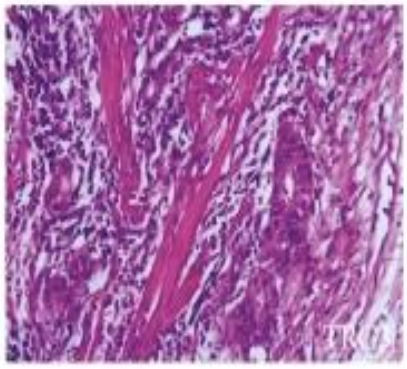
Degree of tumor regression is also an important prognostic factor. The routine use of neo adjuvant therapy for locally advanced rectal cancer has led to the development of grading systems based on the extent of tumor regression. The most commonly used are Mandard and the Dworak systems. Increased grades of regression after neoadjuvant therapy have a good prognosis(81–84)

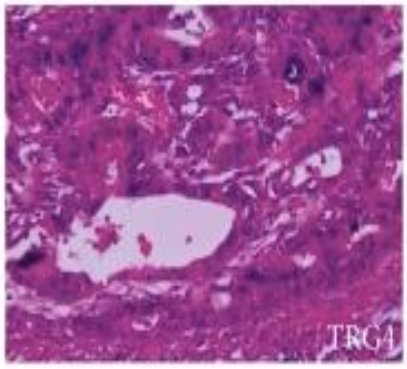
Mandard good responders (TRG1 + TRG2)

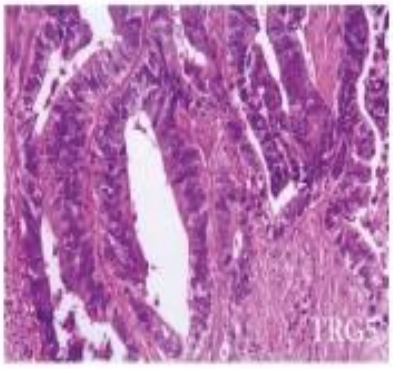




Mandard bad responders (TRG3 + TRG4 + TRG5)

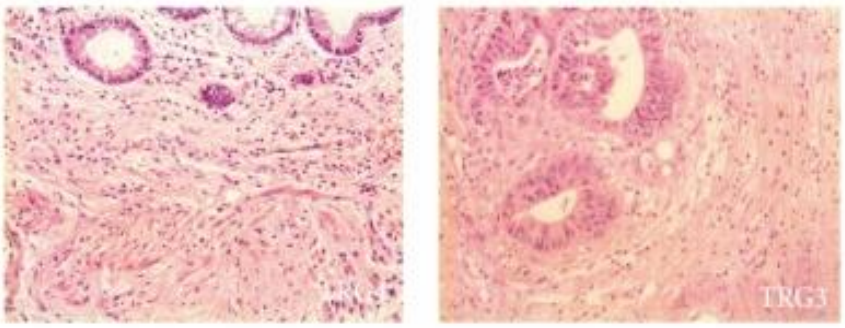




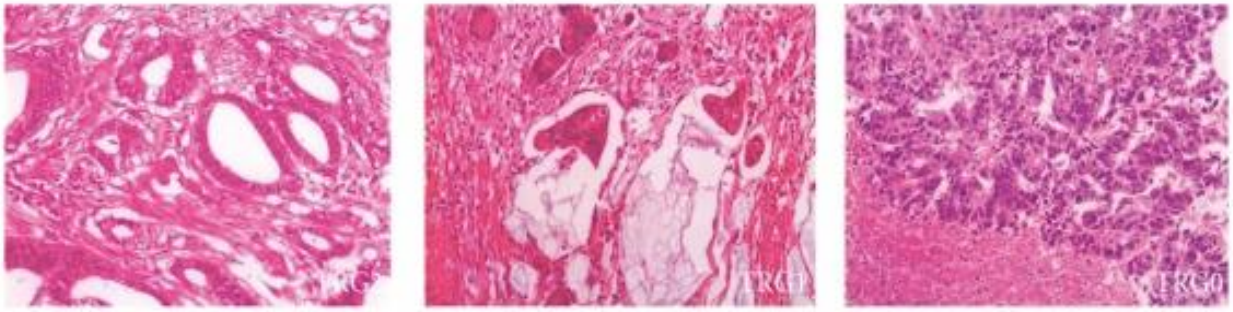


Mandard TRG system	
TRG1	No viable cancer cells, complete response
TRG2	Single cells or small groups of cancer cells
TRG3	Residual cancer outgrown by fibrosis
TRG4	Significant fibrosis outgrown by cancer
TRG5	No fibrosis with extensive residual cancer

Dworak good responders (TRG3 + TRG4)



Dworak bad responders (TRG0 + TRG1 + TRG2)



Dworak TRG system	
TRG0	No regression
TRG1	Dominant tumor mass with obvious fibrosis and/or vasculopathy
TRG2	Dominant fibrotic changes with few tumor cells or groups (easy to find)
TRG3	Very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucus substance
TRG4	No tumor cells, only fibrotic mass (total regression)

Prognostic value of mandard and dworak tumor regression grading in rectal cancer: study of a single tertiary center. Santos MD, Silva C, Rocha A, Matos E, Nogueira C, Lopes C - ISRN Surg (2014)

3.12 SIGNET RING CELL CARCINOMA RECTUM

Signet ring cell carcinoma rectum was first reported by Laufman and Saphir in 1951(85).Signet ring cell carcinoma rectum is one of the rare subtypes of rectal cancer. It accounts for about 1% of subtypes of rectal cancers(86) More than 50% of the tumor cells contain intracytoplasmic mucin displacing the nucleus(87)It is seen in younger age groups ,locally advanced disease at presentation and poor prognosis(88).Poor outcome is stage independent(86). Chances of distant metastasis is high(89). Routes of metastasis are peritoneal, lymphatic and haematogenous. Peritoneal metastasis is common(89,90)

One of its characteristic feature is its late manifestation and majority of them are diagnosed at late stages(91).Delayed diagnosis decreases the chance of resection with curative intent and it can lead to local and distant metastasis(92)

Three factors had been found out for delayed diagnosis of signet ring cell carcinoma rectum(93) :

1. tumor is rare
2. it spreads intramucosally with sparing of rectal mucosa and accounts for less symptoms
3. mimics inflammatory processes

Signet ring cell carcinoma has abundant intracytoplasmic mucin and it displaces

nucleus to the periphery and looks like signet ring. Signet cells can coexist in mucin pools of mucinous adenocarcinoma(94).

K-ras mutation prevalence and p16 and p53 expression are less with signet ring cell carcinoma. B-raf mutation prevalence is high. Higher prevalence of microsatellite instability-high is seen. When compared to other adenocarcinomas, signet ring cell carcinoma fall into an independent subtype(95).

One of the studies done in Indian population had shown that signet ring cell carcinoma had better pathological complete response and better survival. So, whether the histology itself or its late presentation is responsible for poor prognosis is still a debatable question(96).

Median survival is 20 months and five year survival rate is between 10% and 35%(97–99). Some studies showed that early diagnosis is needed to improve outcome(100). Data on the response to preoperative chemo irradiation in signet ring cell carcinoma is less studied(101).

In an Indian study, after preoperative chemo irradiation there was 56% down staging followed by surgery. Among those underwent surgery 65% failed locally and distally. This study shows that signet ring cell carcinoma is an independent poor prognostic factor for an inferior overall survival(102).The Korean National registry also found that signet

ring cell carcinoma have higher grade and bad disease free survival(103).In a German study it has been shown that 65% of signet ring carcinoma were not operable(104).

In a study done in limited population group, preoperative chemo irradiation was associated with significant tumor response in patients with limited lymph node disease. Two different histological responses were seen. Complete response (ypT0N0) or diffuse infiltration of residual tumor cells to bowel wall, mesorectal region and nearby pelvic organs. Radiobiological explanation for this two different histological response is unknown(101).

3.13 MICOSATELLITE INSTABILITY IN RECTAL CANCER

- **Cellular response to Radiotherapy**

  Ionizing radiation causes cell kill by double strand DNA breaks. In response to this, highly complex intracellular molecular pathways are activated and are called DNA damage response (DDR). Activated molecules can be sensors, transducers and effectors of DDR(105).The sensor protein include meiotic recombination 11 (MRE11) complex, trimer of MRE11, RAD50, and NBS1 (XRS2)(106). DDR transducers are ataxia telangiectasia mutated (ATM, TEL1) and ataxia telangiectasia and RAD-3 related proteins.They send damage signal to DDR effectors resulting in cell cycle arrest and may result in repair of the DNA damage.

So cancer cells which don't have these proteins have more chance of death from DNA damage produced by radiation therapy(107,108)

There are different DNA repair mechanisms. Most important are homologous recombination and non-homologous end joining (NHEJ).NHEJ is the main mechanism by which double strand breaks due to radiation are repaired(109).

- **Molecular basis of microsatellite instability**

  Microsatellites are tandemly repeated short DNA sequences throughout the genome. Microsatellite length will be altered by single strand breaks and can result in DNA replication mismatch errors. DNA microsatellite mismatch repair (MMR) pathway is activated and it identifies the error and then substitute with correct base pair. Important proteins that are involved include MLH-1, MSH (MSH-2 and MSH-6) and PMS-2(110). If there is failure to repair these errors in tumors with defective MMR, this will lead to discordant lengths of microsatellite loci between the tumor cell genome and normal cells. Such Microsatellite instability is seen in or approximately 15% of colorectal cancers(111).

  MSI colorectal cancers are usually sporadic, that is with methylation of promoter region of MLH 1. There can be germ line mutation of MLH-1 and/or MSH-2, MSH-6 or rarely PMS-2 in hereditary non-polyposis colorectal cancer (Lynch syndrome). Lynch syndrome is autosomal dominant inheritance of colorectal and

other cancers which includes endometrial, gastric and ovarian origin and they present at an early age usually mid to late forties(112).

MSI colorectal cancers have the following characteristics(112–114)

1. Location is usually proximal
2. poorly differentiated or undifferentiated tumors
3. tumor infiltrating lymphocytes
4. Crohn's disease-like host response with lymphoid aggregates
5. mucinous, signet ring or medullary type histology
6. better prognosis, with hazards ratio for death of 0.65

- **Assessment of microsatellite instability status**

It can be assessed by either immunohistochemistry (IHC) or by polymerase chain reaction (PCR). Sensitivity of PCR is higher(115,116).MSI IHC is simpler and helps to find out MSI status preoperatively from colonoscopic tumor biopsies.

- **Microsatellite instability and Radiation sensitivity**

DNA MMR proteins are directly involved in the DNA damage response after radiation induced double strand breaks. Hence their deficiency may indicate sensitivity to radiotherapy(117). In the context of colon cancers microsatellite instability high has favorable prognosis. But signet ring cell itself is a poor prognostic factor. Hence it is not known whether MSI high signet ring cell carcinoma has a favorable outcome. In a study

done in signet ring cell carcinoma rectum they found one third of them are MSI high and had a better five year survival. However microsatellite instability status does not predict survival in signet ring cell carcinoma rectum(118). In a recent study it was found that mortality due to signet ring cell carcinoma rectum did not differ by MSI status(119).

3.14 RADIOTHERAPY PORTALS IN RECTAL CANCER

Radiotherapy field encompasses all possible areas of local recurrence. Mostly recurrences are seen in pelvic soft tissue, pelvic nodes, anastomotic site and perineum(120).In T4 tumors there are chances of recurrence in anterior structures. The lymph nodal groups included are the internal iliac and the obturator . The external iliac lymph nodes are included only when anterior tumor extension or involvement of adjacent structures.

Conventional radiotherapy

Pelvic radiotherapy can be given by a four field box technique or by 3-field approach (Two laterals and a PA field).

- **Field borders**

Whole Pelvis

1. **AP-PA**

Superior: L5-S1 to encompass the attachment of the posterior peritoneum

Lateral: 1.5 cm beyond the widest bony margins of the true pelvis to encompass the possible lateral extension and the internal iliac chain.

Inferior: 3-3.5cm beyond the lower extent of the tumor. It can be located either by direct palpation if it is a lower growth, or with the aid of rectal contrast or an endoscopically placed clip.

For post operative cases, in cases of post LAR it is placed 3 cm beyond the region of the anastomosis, or in cases of post APE placed beyond the anal verge to encompass the perineal scar.

The inguinal nodes are included only in case of extension into the anal canal or involvement of the anterior structures.

The para aortic nodes are not included in the portals as it is considered to be metastatic disease.

2. **Lateral fields**

Anterior: T2 and T3 lesions it is placed at the posterior margin of the pubic symphysis to include the internal iliac nodes.

For T4 lesions: Usually placed at the anterior margin of the pubic symphysis to include the external iliac nodes.

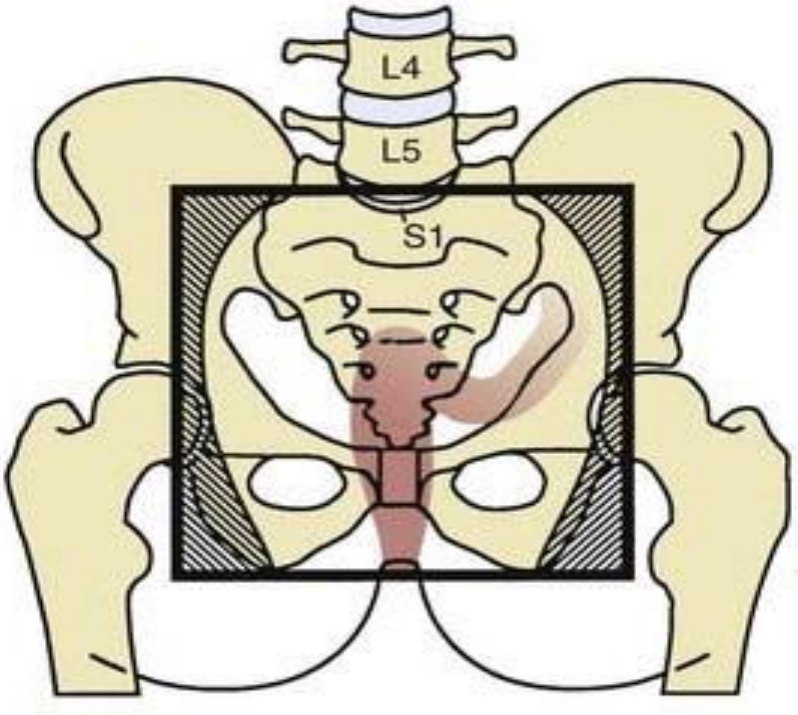
Posterior: entire sacral hollow

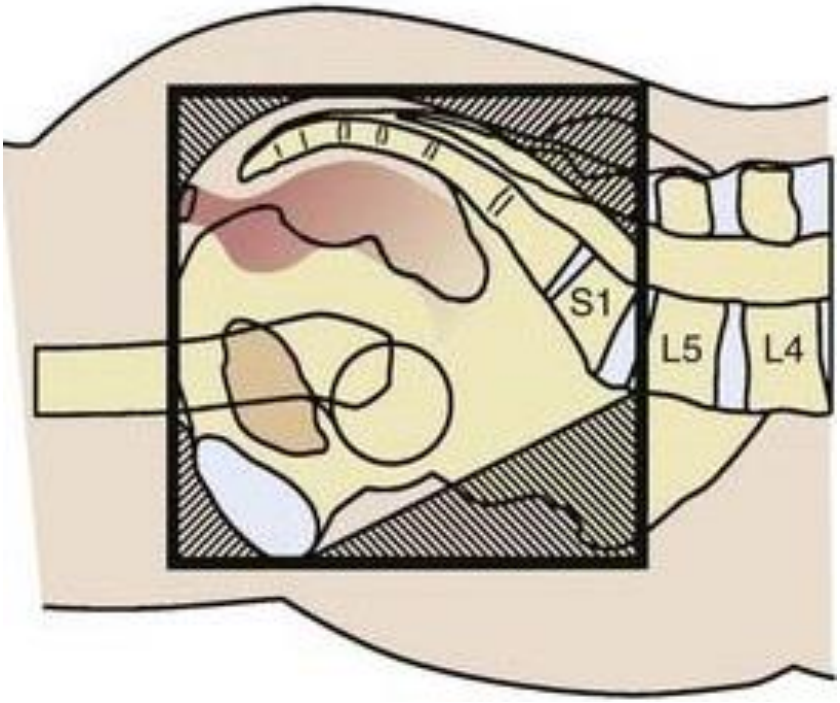
Superior and inferior: same as that of AP/PA fields.

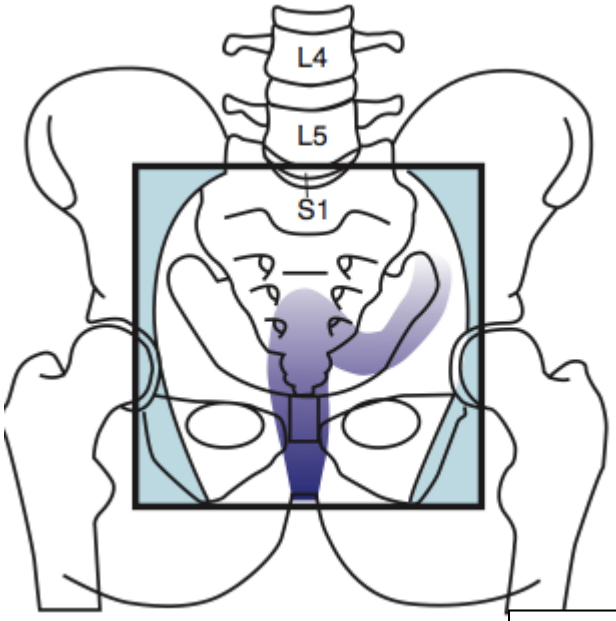
Boost field

Primary tumor with a 2 cm margin. The nodes are not routinely included in the boost field.

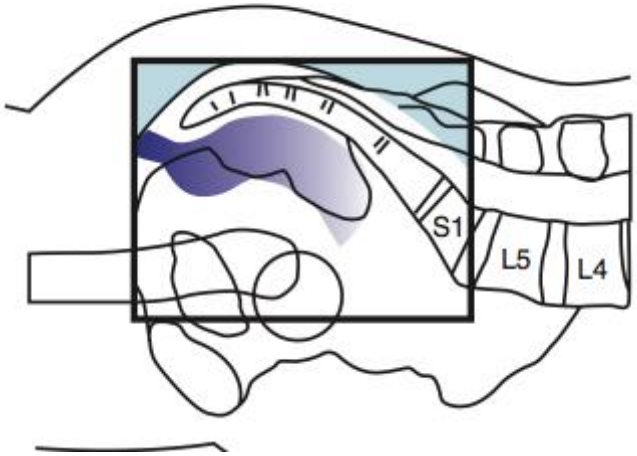
Manual blocks are placed to shield the small intestine as well as the soft tissue posterior to the sacrum.

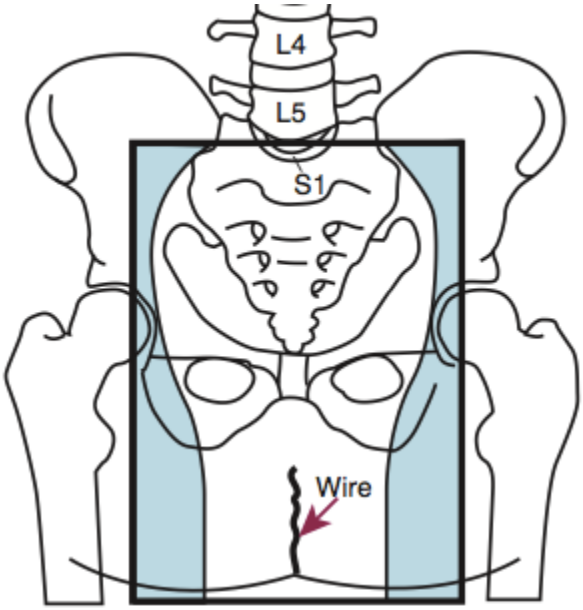



S1
L5
L4

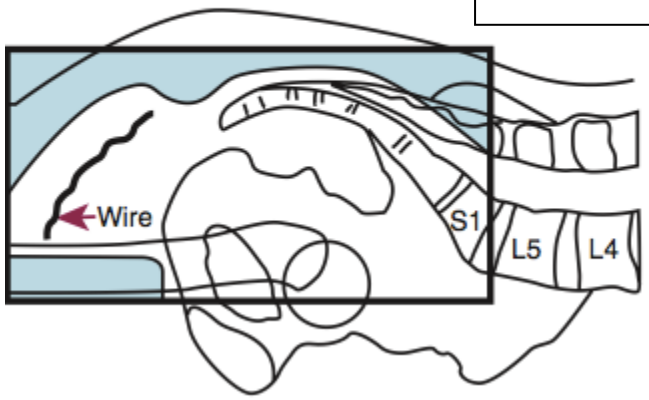


Portals used post LAR





Portals used post APE



Conformal radiotherapy

Conformal radiotherapy helps in sparing the normal tissue without compromising the dose delivered to the target volumes. The GTV comprises of GTV-Tumor and the GTV-Node which is seen both clinically as well as on imaging.

The CTV includes the entire mesorectum, presacral space as well as the obturator, internal iliac groups. The common iliac and the external iliac are not routinely included in all cases.

The PTV is the expansion of the CTV to account for organ motion and set up errors.

The OAR's are routinely contoured and are kept below their threshold limits.

Guidelines in rectal IMRT(121)

CTV Rectum: Rectal GTV +1.5 cm radially, +2.5 cm craniocaudally)

CTV Nodes: Nodal GTV + 1.5 cm symmetrical expansion

Uninvolved iliac vessels + 1.0 cm = CTV (include external iliac if T4)

Presacral lymphatic CTV: contouring from mid S1-S5 and 8 mm tissue anterior to the anterior border of the sacral bone

The mesorectum and perirectal lymphatics CTV :

Posterior Border: anterior border of the sacrum and gluteus maximus

Lateral Border: ileum, piriformis and obturator muscles

Anterior Border: should overlap by 1 cm into the bladder, vagina or prostate

PTV: expanding all of the above by 0.5 cm symmetrically

IMRT reduces dose to normal tissues. It has concerns regarding dose heterogeneity and geographical miss as there can be differences in the position of the target

4. MATERIALS AND METHODS

22 patients with signet ring cell carcinoma rectum who have undergone preoperative - long course chemo irradiation therapy (LCCRT) were enrolled for this study after clearance from the institution review board. The standard work up of rectal cancer includes biopsy, MRI pelvis ,CEA ,CT thorax and abdomen or chest X ray and USG abdomen and pelvis is done to rule out distant metastases. Patients who are non metastatic were included in the study. All the biopsy proven patients had diagnostic MRI pelvis and MSI status assessment using immunohistochemistry before the initiation of radiation therapy. All patients received preoperative long course chemo radiotherapy to a dose of 50.4 Gy. They also receive concurrent chemotherapy with Capecitabine (825 mg/m2) twice daily on days of radiation therapy. After 6 weeks of radiotherapy, response assessment was done using MRI pelvis. Patients who were operable after radiotherapy underwent Total Mesorectal Excision. Radiotherapy response was assessed by comparing pretreatment MRI with post radiation therapy MRI down staging, pathological response and correlation with MSI status.

MRI PELVIS Protocol

Standard high resolution (HR) T2 weighted MRI of the pelvis will be performed in sagittal, oblique axial (perpendicular to the rectum) and oblique coronal (parallel to the rectum) planes. Diffusion weighted (DWI) MR images will be obtained in the same oblique axial plane as T2 weighted high resolution images using respiratory triggered, single shot, echo-planar-imaging with b-values of 0, 100,and 800 sec/mm2.

Sequence	Slice thickness (mm)	FOV (cm)	Acquisition time (min)
T2W axial	6	375	2
T2W SPAIR axial	6	375	2
T1W axial	6	380	1.37
T2W HR coronal	3	230	2.43
T2W HR sagittal	3	220	2.23
T2W HR axial	3	230	3.19
Single shot EPI DWI transverse	4	380	3.15

Tumor regression grading

In our center, we use Mandard tumor response grading system to assess TRG.

Tumor response was graded as follows:

TRG 1 - complete regression with absence of residual cancer and fibrosis extending through the wall (Complete response)

TRG 2 – rare residual tumor cells scattered throughout the fibrosis (Near complete response)

TRG 3 - predominant fibrosis but increase in the number of cancer cells (Moderate response)

TRG 4 - residual cancer cells outgrowing the fibrosis (Minimal response)

TRG 5 - absence of regressive changes (No response).

Immunohistochemistry protocol to assess MSI status

1. Paraffin embedded tissue sections will be cut at 4μ thickness and floated in poly L-lysine coated slides and incubated overnight at 37˚C.

2. These slides will be then treated with 4% milk solution for 10 minutes to eliminate the hydrophobic effect and give positive charge to the slides.

3. Then the slide labels will be bar coded and the labeled slides will be loaded in Ventana Benchmark XT autostainer (a fully automated immunostainer).

4. Individual protocols have been designed in the software attached to the machine for each marker. Specific protocols will be selected according to the marker.

5. A standard protocol will be used for most of the markers with a minimal variation for few individual markers. The steps included in this protocol are as follows:

a. Deparaffinization

b. Liquid coverslip application.

c. Heat induced antigen retrieval by treating with standard CC1 solution (pH patent with the company) for one hour at 90˚C.

d. Then the primary antibody will be added and incubated for 40 minutes @ 37˚C.

e. Then the secondary antibody (Multimer) will be added and incubated for 8 minutes.

f. Finally the slides will be counterstained with Haematoxylin and incubated for 8 minutes, followed by incubation with the bluing reagent for 4 minutes. (From antigen retrieval till counterstaining, in between every step the slides were washed with reaction buffer. The whole process is automated). Then the slides will be brought to 80% alcohol (2 changes) to remove the liquid cover slip and then dried and mounted in DPX.

Inclusion criteria:

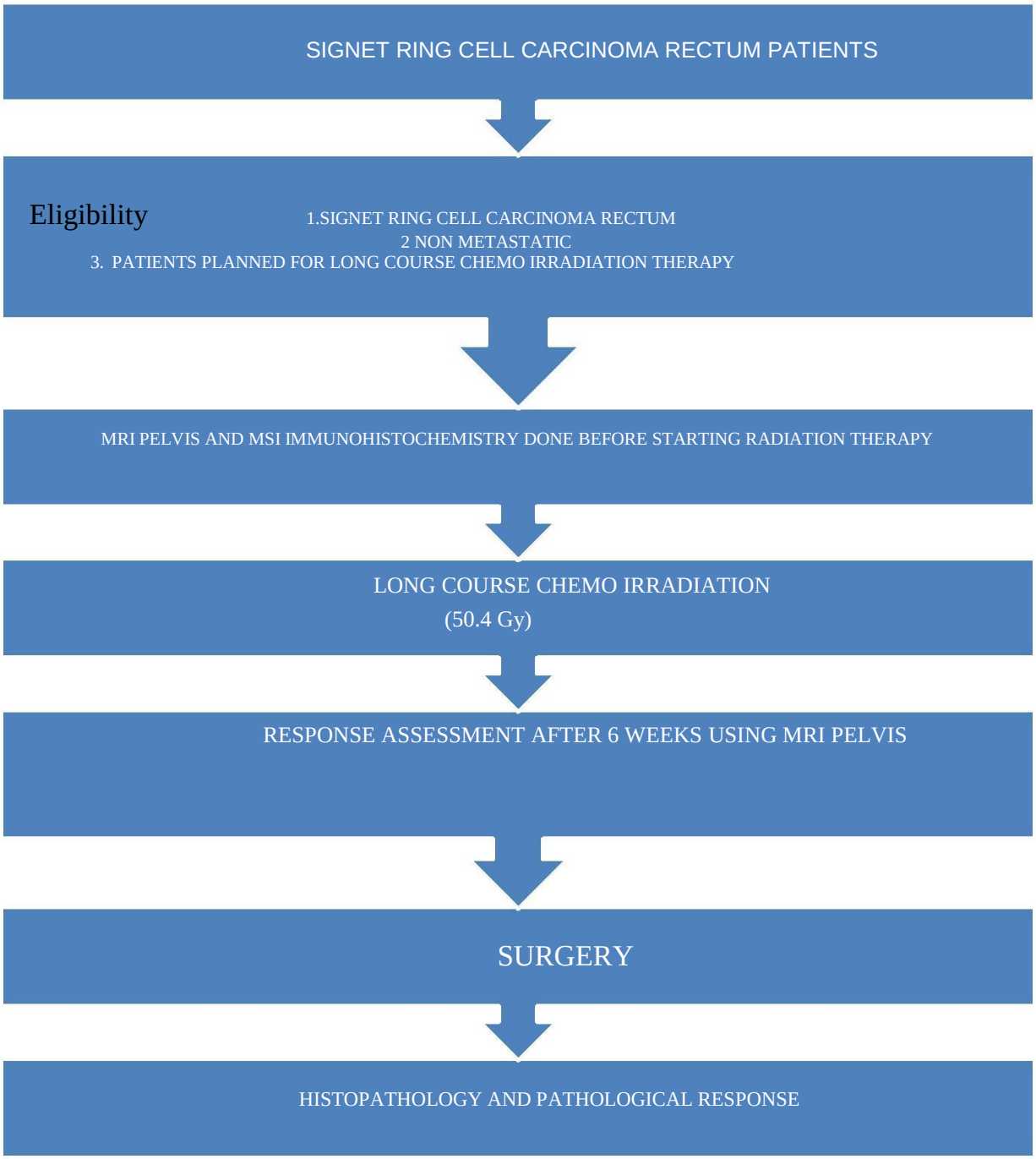
1. Signet ring cell carcinoma rectum
2. Planned for neoadjuvant radiotherapy along with concurrent chemotherapy (Concurrent Capecitabine)
3. No prior pelvic malignancies
4. No history of prior radiation to the abdomen/pelvis
5. Not a known case of myelodysplastic syndrome/myelofibrosis

Exclusion criteria

1. Metastatic disease
2. Pregnant women

The proposed study was presented in the Institutional Review Board (IRB) which includes Research committee and Ethics Committee and approval was obtained (copy enclosed). The patients were selected based on the inclusion and exclusion criteria.

Detailed diagrammatic Algorithm of the study



Sample size

There were total of 22 patients who were included in the study during a period of 2013 to 2016. 8 patients were prospective and 14 patients were retrospective.

5. RESULTS

Patient characteristics

There were 13 male patients and 9 female patients. 59.1% of the patients (13 patients) were between 20 to 40 years. The mean age group was 38 years, ranging from 18 to 62 years. 90.9% of them were married. All patients had ECOG performance score 1.

Table 1: Patient characteristics

Variables	Frequency (n =22)	Percentage (%)
Age(years)	Mean -38(Range 18-62)	
<20years	1	4.5%
20-40years	13	59.1%
>40years	8	36.4%
Sex		
Male	13	59.1%
Female	9	40.9%
Marital status		
Married	20	90.9%
Unmarried	2	9.1%

ECOG Performance score 0 1 2 3 4 5	 0 22 0 0 0 0	 0 100% 0 0 0 0

Fig : 1 : Distribution of age

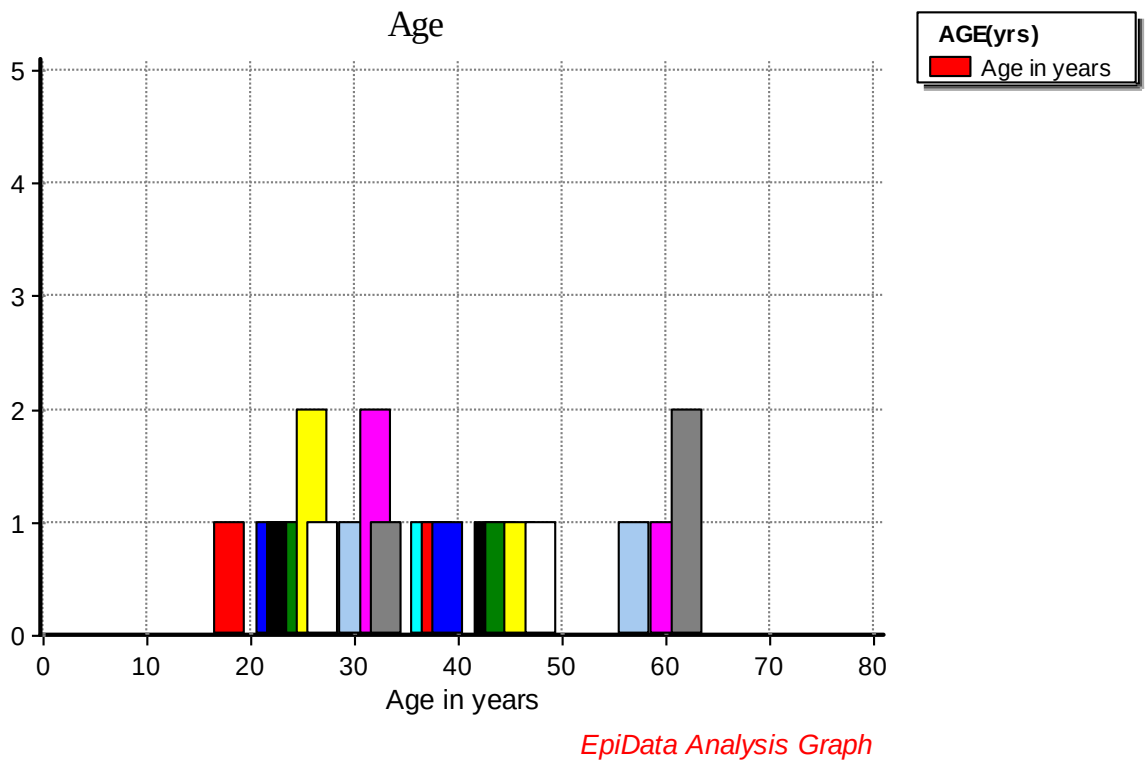


Fig 2 : Distribution of sex

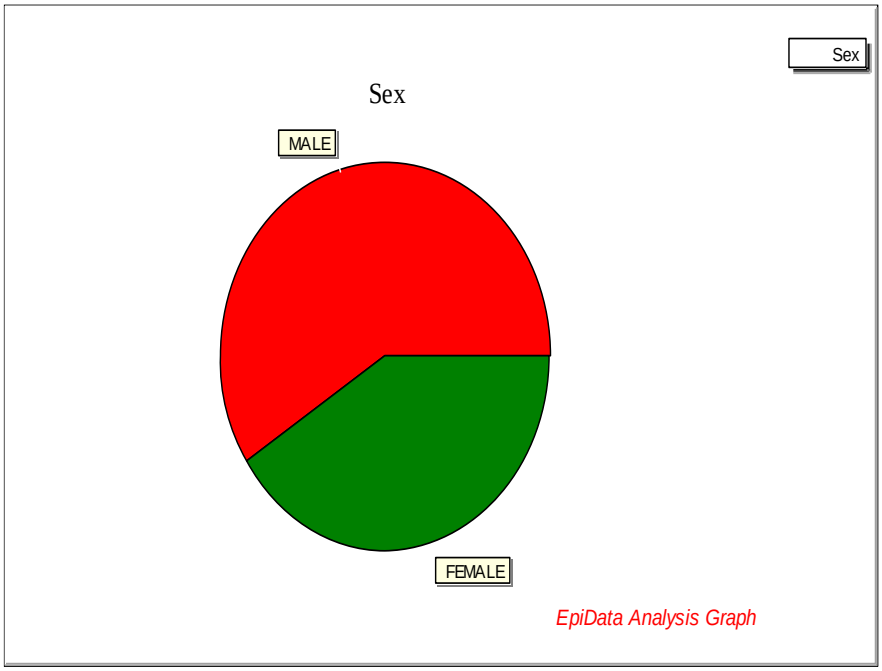
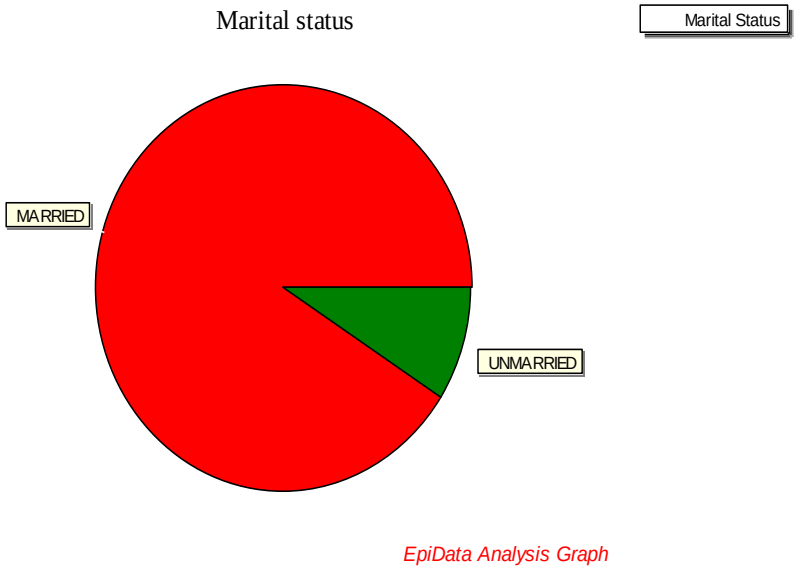


Fig 3 : Distribution of Marital status



Disease characteristics at the time of diagnosis

72.7% of the tumors were located within 5 cm from anal verge. 59.1% had normal CEA at the time of diagnosis. 72% were T3 lesions and 63.6% had N2 disease. All the patients had signet ring cells. In 45.5% of patients there were mucin component also along with signet ring cells. 40.9% had diversion stoma before the initiation of treatment.

Table 2 : Disease characteristics at diagnosis

Characteristics	N(22)	Percentage(%)
Distance from anal verge		
0-5cm	16	**72.7%**
5-10cm	6	**27.3%**
≥10cm	0	**0**
CEA at diagnosis		
<5ng/ml	13	**59.1%**
≥5ng/ml	9	**40.9%**

T –stage at diagnosis		
T1	0	**0%**
T2	2	**9.1%**
T3	16	**72.7%**
T4	4	**18.2%**
N – stage at diagnosis		
N0	1	**4.5%**
N1	7	**31.8%**
N2	14	**63.6%**
HISTOLOGY		
Signet ring cell	12	**54.5%**
Signet ring + mucin	10	**45.5%**
Diversion		
Yes	**9**	**40.9%**
No	**13**	**59.1%**

Figure 4 : Distance from anal verge

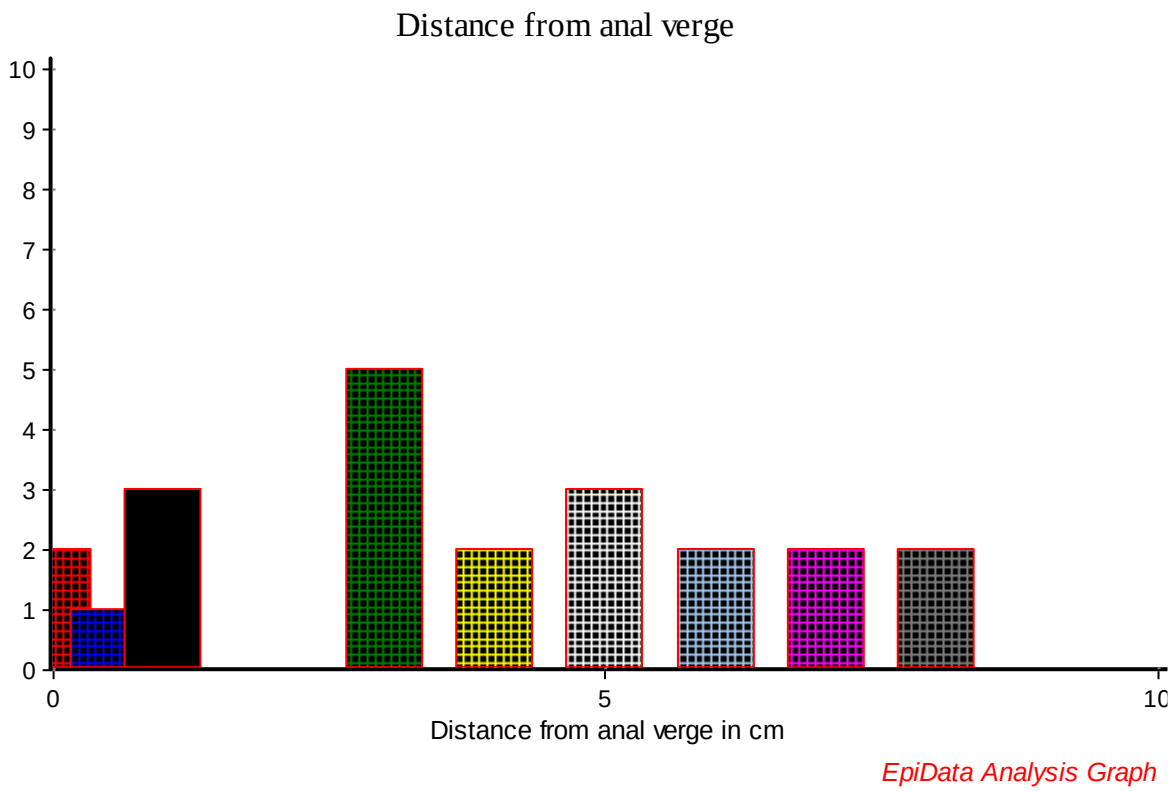


Figure 5 : T stage

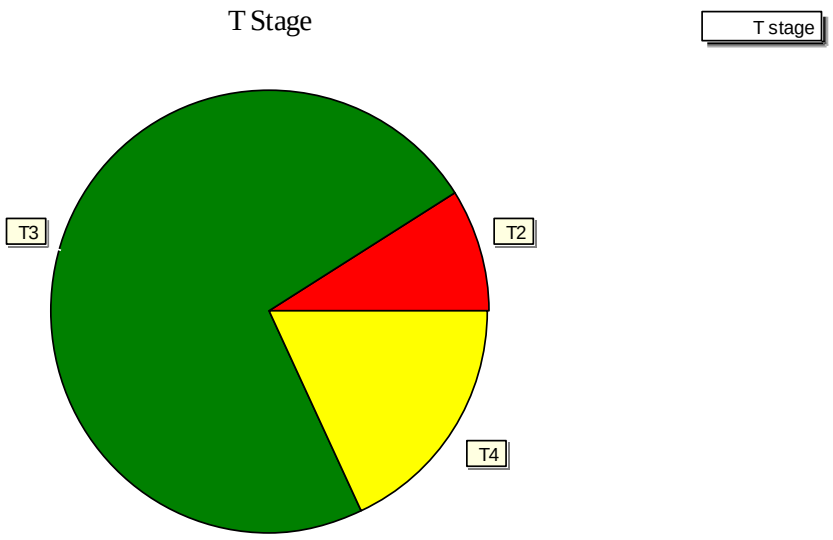


Figure 6 : N stage

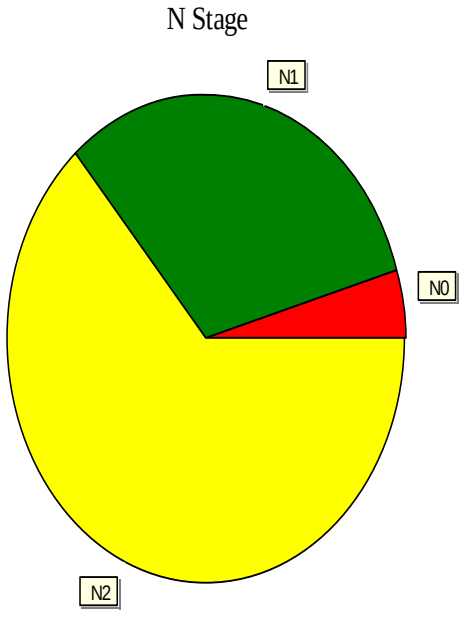
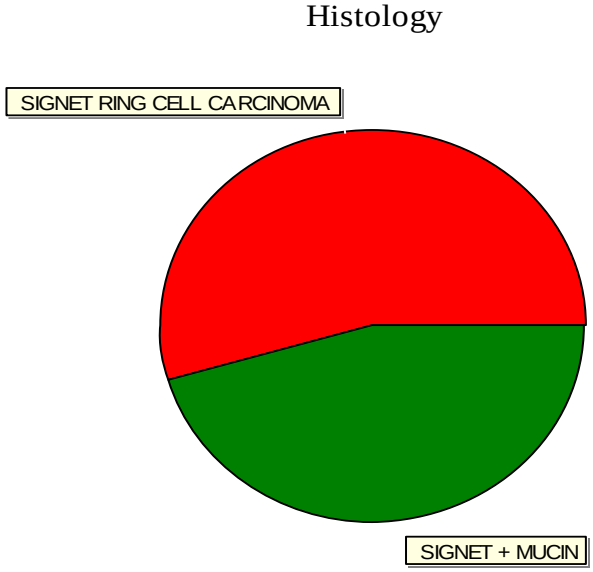
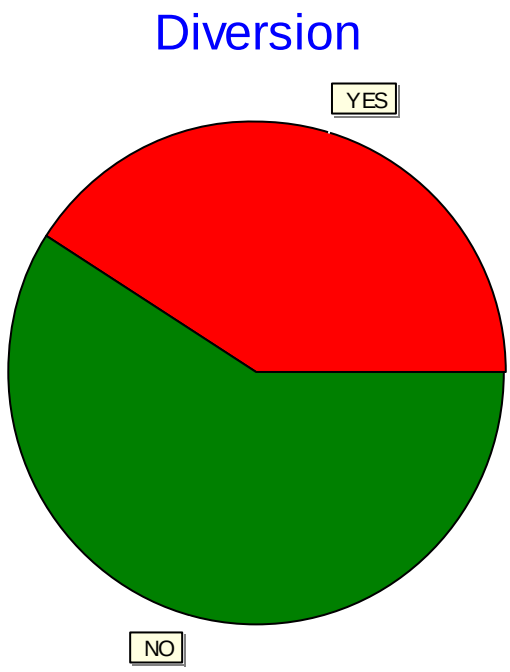


Figure 7 : Histology



EpiData Analysis Graph

Figure 8 : Diversion



EpiData Analysis Graph

Details of chemo irradiation

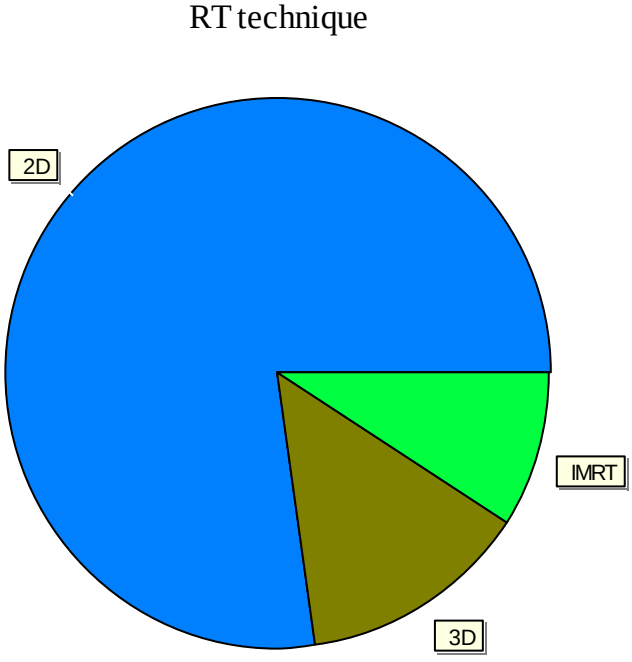
77.3% received radiation via two dimensional four field box technique. 13.6% received 3DCRT and 9.1% received by IMRT. Patients who underwent 2D, 3D conformal RT and one patient who underwent IMRT received 50.4Gy in 28 fractions (Phase 1: 45Gy in 25 fractions and Phase II: 540cGy in 3 fractions). Second patient who underwent IMRT received simultaneous integrated boost of 45Gy in 25 fractions to CTV 45 and 50.4Gy in 25 fractions to CTV 50.4. Out of 22 patients, 21 patients had concurrent Capecitabine (825mg/sq.m twice daily on days of radiation therapy) and one patient did not receive concurrent Capecitabine due his co morbid illness.

Table 3 : Details of chemo irradiation therapy

Characteristics	N(22)	Percentage (%)
Dose :		
50.4Gy in 28 fractions	21	**95.5%**
50.4Gy in 25 fractions (SIB)	1	**4.5%**
Technique		
2D	17	**77.3%**
3DCRT	3	**13.6%**
IMRT	2	**9.1%**

Concurrent Capecitabine		
Yes	**21**	**95.5%**
No	**1**	**4.5%**

Figure 9: RT Technique



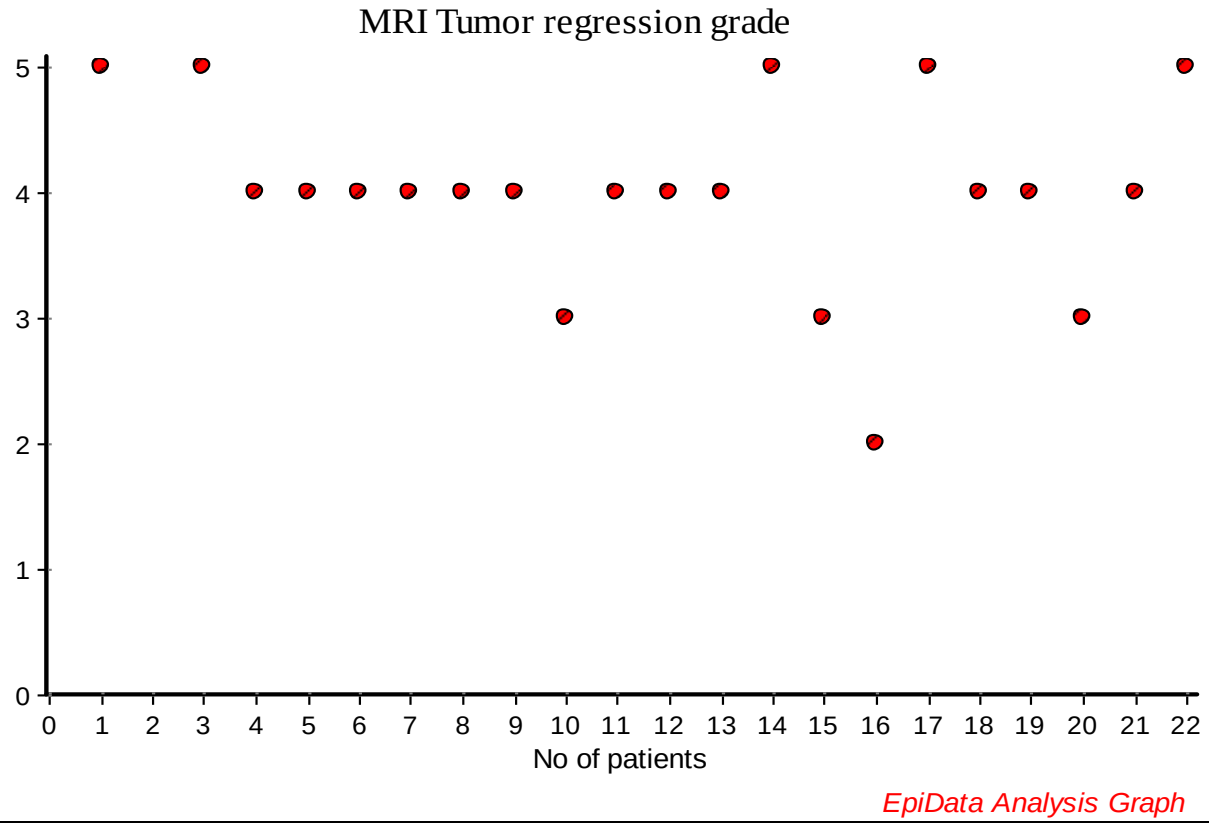
MRI Tumor regression grade

One patient did not have post radiation therapy response assessment MRI since there was clinical progression. 57.1 % patients showed only minimal response in MRI after 6 weeks of long course radiation therapy. None of the patients had complete MRI response.

MRI TRG	N=21	Percentage (%)
1= Complete response	0	0%
2= Near complete response	1	4.8%
3= Moderate response	3	14.3%
4=Minimal response	12	57.1%
5=No response	5	23.8%

Table 4 : MRI Tumor regression grade

Figure 10 : MRI Tumor regression grade



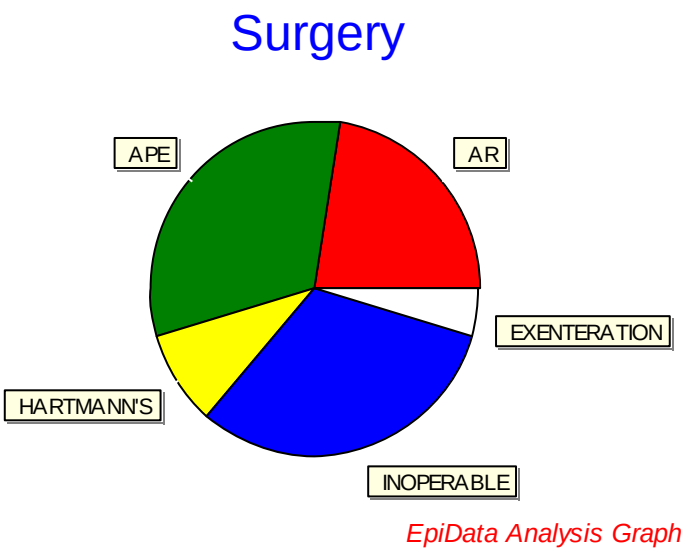
DETAILS OF SURGERY

Among 22 patients seven (31.8%) were inoperable. 31.8% had Abdominoperineal resection and 22.7% had Anterior resection.

Table 5: Details of Surgery

DETAILS OF SURGERY	N =22	Percentage (%)
Anterior Resection	5	**22.7%**
APE	7	**31.8%**
Hartmann's Operation	2	**9.1%**
Exenteration	1	**4.5%**
Inoperable	7	**31.8%**

Figure 11: Details of Surgery



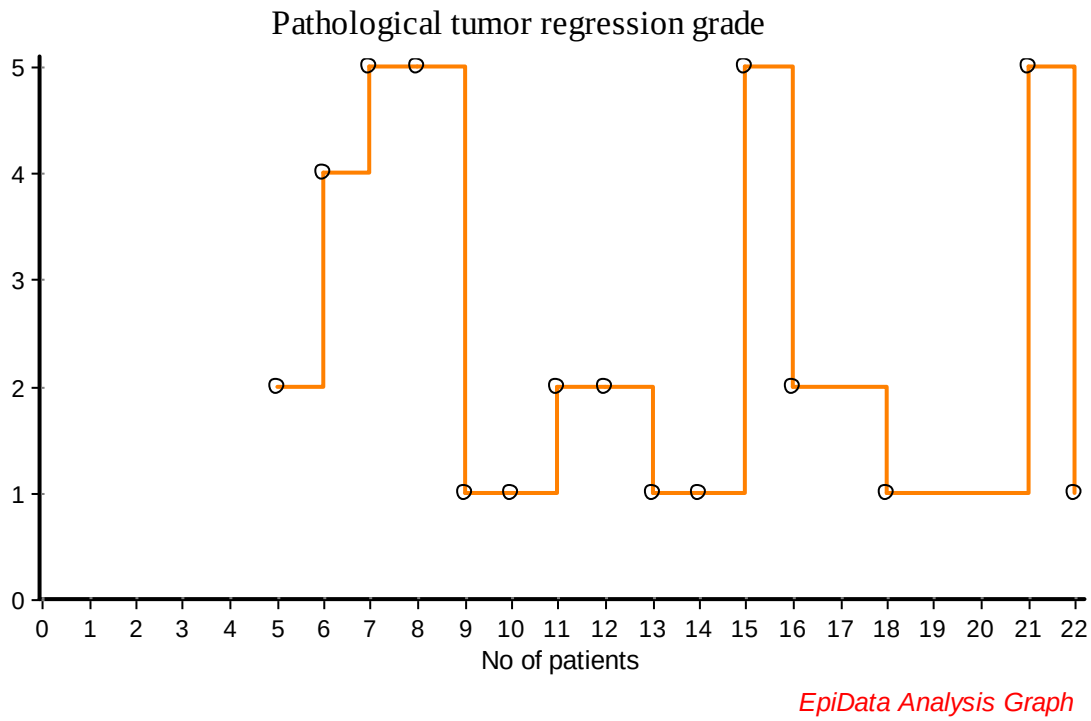
Pathological tumor regression grade

Among the 15 patients who underwent surgery, post operative histopathological examination revealed, 40% had complete response, 26.7% had near complete response and 26.7% had no response.

Table 6: Pathological tumor regression grading

PATHOLOGICAL TRG	N = 15	Percentage (%)
1= Complete response	6	40%
2= Near complete response	4	26.7%
3= Moderate response	0	0
4=Minimal response	1	6.6%
5=No response	4	26.7%

Figure 12 : Pathological Tumor regression grade

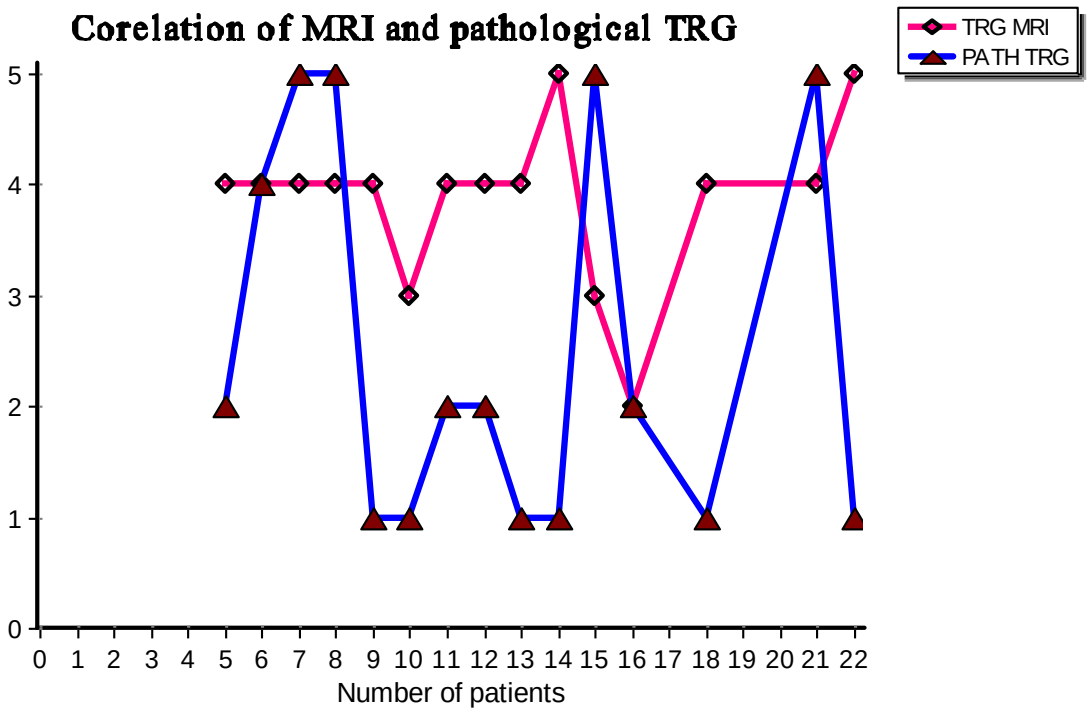


5.1 CORRELATION BETWEEN MRI TRG AND PATHOLOGICAL TRG

No of patients	MRI TRG	HPE TRG
1	4	2
2	4	4
3	4	5
4	4	5
5	4	1
6	3	1
7	4	2
8	4	1
9	5	1
10	3	5
11	2	2
12	4	1
13	4	5
14	5	1
15	4	2

Table 7: Correlation between MRI TRG and Pathological TRG

Figure 13: Correlation between MRI TRG and Pathological TRG



MSI STATUS

MSI Immunohistochemistry was done for 17 patients. MSI was negative for all the 17 patients. Hence MSI status and radiotherapy response could not be correlated in Signet ring Cell Carcinoma Rectum.

5.2 CHARACTERISTICS OF PATIENTS WITH COMPLETE RESPONSE

Table No: 8: Characteristics of patients with complete response

Patient	1	2	3	4	5	6
Age in years	23	46	26	26	27	32
Sex	Female	Male	Female	Male	Male	Female
Pretreatment CEA (ng/ml)	< 5	<5	<5	<5	≥5	<5
Location from anal verge in cm	5	7	8	1	3	3
Diversion	No	No	No	Yes	No	No
T stage	T3	T3	T3	T2	T3	T4
N stage	N2	N2	N2	N1	N2	N2
CRM(pre RT MRI)	Involved	Involved	Involved	Involved	Involved	Involved
RT Dose in Gy	50.40	50.40	50.40	50.40	50.40	50.40
Capecitabine	Yes	Yes	Yes	Yes	Yes	Yes
RT technique	2D	3D	2D	2D	2D	3D
Post RT CEA (ng/ml)	<5	<5	<5	<5	<5	<5
MRI TRG	4	3	4	5	4	5

Post operative margin Status	Negative	Negative	Negative	Negative	Negative	Negative
MSI status	Not done	Negative	Negative	Negative	Negative	Negative
Surgery	AR	AR	AR	APE	APE	APE
Pathological TRG	1	1	1	1	1	1

Among 15 patients who underwent surgery, 6 had complete pathological response. Median age group was 30 years.50% were males and 50% females. 67% of them had lower rectal tumors. 83% had normal CEA. 67% had T3 disease and 16% had T4 disease and 83% had N2 disease. CRM was involved all the 6 patients. MSI was negative for 5 patients. All patients received long course chemo irradiation with a dose 50.40Gy in 28 fractions with concurrent Capecitabine. Reassessment MRI done after 6 weeks showed that 50% had minimal response, 33.3% had no response and remaining had moderate response. Based on MRI findings and clinical assessment, 50% underwent anterior resection and 50% underwent abdominoperineal excision. Histopatholgical examination showed all had complete response (ypT0N0).

6. DISCUSSION

Signet ring cell carcinoma of the rectum is a rare subtype of rectal cancer in younger populations and is associated with poor prognosis. While the standard of care in any locally advanced rectal cancer is long course chemo irradiation followed by total mesorectal excision, the same approach does not give similar outcomes in Signet ring Cell Carcinoma rectum. Current literature supports the above said management of rectal cancer; however specific data on outcomes like down staging following neoadjuvant chemo irradiation in signet ring cell carcinoma rectum is lacking. There are few anecdotal reports of poor response seen in of signet ring cell carcinoma of rectum to radiation therapy. We found similar outcomes when MRI was done 6 weeks since completing long course chemo irradiation. However we observed an unusual and rarely reported outcome where 6/15 (40%) patients had shown complete pathological response.

Most of the studies in rectal cancer showed that signet ring cell carcinoma is seen in younger age group. In our study also, 60% of the patients were less than 40 years, mean age was 38 years and predominantly seen in males.

In our study, 72.7% of the tumors were low rectal tumors and pretreatment CEA was normal in 59.1%. 72% were T3 lesions and 63.6% had N2 disease. Hence majority patients belong to the category of “The Bad” rectal cancers and a few were “The Ugly” rectal cancers.

Elmashad etal, Sathyakumar etal showed that after preoperative chemo irradiation, a reassessment MRI pelvis after 6 weeks showed down staging by achieving both tumor and lymph node down staging in rectal cancers. In our study we did post radiation therapy reassessment MRI pelvis which showed 57.1 % patients had minimal response and 23.8% had no response. Among these 21 patients who had post radiation therapy MRI pelvis, 15 underwent surgery based on MRI response assessment and clinical examination. Though most patients had only minimal response in reassessment MRI pelvis, based on Surgeon's clinical assessment, many were operable and had undergone surgery. Surgical pathology showed that 40% had complete response, 26.7% had near complete response and 26.7% had no response. This result was irrespective of the reassessment MRI pelvis response. Even patients who did not show any response in reassessment MRI, showed histopathological complete response. Hence the predictive role of response assessment after long course chemo irradiation with MRI in signet ring cell carcinoma rectum needs to be cautiously interpreted.

Data on microsatellite instability and radiation response in signet ring cell carcinoma rectum is lacking. In our study MSI IHC could be done only for 17 patients and all were negative for MSI. Hence no correlation between MSI and radiation response could be inferred in this study. Kakar etal showed that about one third of signet ring cell carcinomas of the colorectum have microsatellite instability, however it was not a significant predictor of survival in signet ring cell carcinoma of the colorectum.

The major limitation of our study was limited cohort of this rare subtype of signet ring cell carcinoma rectum. Owing to time constraints we could not correlate the follow up data on local control and disease free survival and overall survival. In this study MSI status was assessed using Immunohistochemistry. PCR is considered to be more sensitive and specific test. However an interesting observation of this study revealed that 40% had complete histopathological response even though their MRI predicted poor response to radiation therapy. Hence the predictive role of MRI in down staging the tumor after radiation therapy in signet ring cell carcinoma rectum needs to be evaluated more extensively. Furthermore, bad biology of signet ring cell carcinoma requires a new paradigm which includes molecular and genetic staging, and also aggressive treatment strategies.

7. CONCLUSION

The predictive value of MRI down staging in Signet Ring Cell Carcinoma Rectum following neoadjuvant long course chemo irradiation therapy is not always in concurrence and needs to be re evaluated. The pathological complete response rate in these tumors relatively matches the response rates as seen in non signet ring cell types. Hence long course chemo irradiation still plays a significant role in the management of these tumors. MSI status with IHC technique may be suboptimal and it should preferably be assessed using PCR techniques in future studies.

8. BIBLIOGRAPHY

1. Stewart, B. and Wild, C.P. (eds.), International Agency for Research on Cancer, WHO. World Cancer Report 2014 | The Health Well.

2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015 Mar;65(2):87–108.

3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011 Apr;61(2):69–90.

4. NATIONAL CENTRE FOR DISEASE INFORMATICS AND RESEARCH : Three Year Report of PBCR 2009-2011 [Internet]. [cited 2015 Nov 7]. Available from: http://www.ncrpindia.org/ALL_NCRP_REPORTS/PBCR_REPORT_2009_2011/ALL_CONTENT/Main.htm

5. Mohandas KM. Colorectal cancer in India: controversies, enigmas and primary prevention. Indian J Gastroenterol Off J Indian Soc Gastroenterol. 2011 Feb;30(1):3–6.

6. Mohandas KM, Desai DC. Epidemiology of digestive tract cancers in India. V. Large and small bowel. Indian J Gastroenterol Off J Indian Soc Gastroenterol. 1999 Sep;18(3):118–21.

7. Amersi F, Agustin M, Ko CY. Colorectal cancer: epidemiology, risk factors, and health services. Clin Colon Rectal Surg. 2005 Aug;18(3):133–40.

8. Laskar RS, Talukdar FR, Mondal R, Kannan R, Ghosh SK. High frequency of young age rectal cancer in a tertiary care centre of southern Assam, North East India. Indian J Med Res. 2014 Feb;139(2):314–8.

9. Cancer Statistics Review, 1975-2011 - Previous Version - SEER Cancer Statistics Review [Internet]. [cited 2016 Aug 14]. Available from: http://seer.cancer.gov/archive/csr/1975_2011/

10. Janout V, Kollárová H. Epidemiology of colorectal cancer. Biomed Pap Med Fac Univ Palacký Olomouc Czechoslov. 2001 Sep;145(1):5–10.

11. de Jong AE, Morreau H, Nagengast FM, Mathus-Vliegen EMH, Kleibeuker JH, Griffioen G, et al. Prevalence of adenomas among young individuals at average risk for colorectal cancer. Am J Gastroenterol. 2005 Jan;100(1):139–43.

12. Grande M, Milito G, Attinà GM, Cadeddu F, Muzi MG, Nigro C, et al. Evaluation of clinical, laboratory and morphologic prognostic factors in colon cancer. World J Surg Oncol. 2008 Sep 8;6:98.

13. Winawer SJ, Zauber AG, Gerdes H, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Risk of colorectal cancer in the families of patients with adenomatous polyps. National Polyp Study Workgroup. N Engl J Med. 1996 Jan 11;334(2):82–7.

14. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol. 2001 Oct;96(10):2992–3003.

15. Nooyi SC, Murthy NS, Shivananjaiah S, Sreekantaiah P, Mathew A. Trends in rectal cancer incidence--Indian scenario. Asian Pac J Cancer Prev APJCP. 2011;12(8):2001–6.

16. Wu S, Feng B, Li K, Zhu X, Liang S, Liu X, et al. Fish consumption and colorectal cancer risk in humans: a systematic review and meta-analysis. Am J Med. 2012 Jun;125(6):551–559.e5.

17. A case-control study on diet and colorectal cancer from Mumbai, India [Internet]. [cited 2016 Jun 26]. Available from: https://www.researchgate.net/publication/26777134_A_case-control_study_on_diet_and_colorectal_cancer_from_Mumbai_India

18. Solan P, Davis B. Anorectal anatomy and imaging techniques. Gastroenterol Clin North Am. 2013 Dec;42(4):701–12.

19. Heald RJ, Moran BJ. Embryology and anatomy of the rectum. Semin Surg Oncol. 1998 Sep;15(2):66–71.

20. Shihab OC, Moran BJ, Heald RJ, Quirke P, Brown G. MRI staging of low rectal cancer. Eur Radiol. 2009 Mar;19(3):643–50.

21. Dewhurst CE, Mortele KJ. Magnetic resonance imaging of rectal cancer. Radiol Clin North Am. 2013 Jan;51(1):121–31.

22. Huebner RH, Park KC, Shepherd JE, Schwimmer J, Czernin J, Phelps ME, et al. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. J Nucl Med Off Publ Soc Nucl Med. 2000 Jul;41(7):1177–89.

23. Chun H-K, Choi D, Kim MJ, Lee J, Yun SH, Kim SH, et al. Preoperative staging of rectal cancer: comparison of 3-T high-field MRI and endorectal sonography. AJR Am J Roentgenol. 2006 Dec;187(6):1557–62.

24. AJCC Cancer Staging Manual | Stephen Edge | Springer [Internet]. [cited 2016 Aug 14]. Available from: http://www.springer.com/in/book/9780387884400

25. Prolongation of the disease-free interval in surgically treated rectal carcinoma. Gastrointestinal Tumor Study Group. N Engl J Med. 1985 Jun 6;312(23):1465–72.

26. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med. 1991 Mar 14;324(11):709–15.

27. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet Lond Engl. 1986 Jun 28;1(8496):1479–82.

28. Arbman G, Nilsson E, Hallböök O, Sjödahl R. Local recurrence following total mesorectal excision for rectal cancer. Br J Surg. 1996 Mar;83(3):375–9.

29. Kapiteijn E, Putter H, van de Velde CJH, Cooperative investigators of the Dutch ColoRectal Cancer Group. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. Br J Surg. 2002 Sep;89(9):1142–9.

30. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol Off J Am Soc Clin Oncol. 2012 Jun 1;30(16):1926–33.

31. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo L-J, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol. 2010 Sep;11(9):835–44.

32. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ. 2006 Oct 14;333(7572):779.

33. Taylor FGM, Quirke P, Heald RJ, Moran BJ, Blomqvist L, Swift IR, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin

predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. J Clin Oncol Off J Am Soc Clin Oncol. 2014 Jan 1;32(1):34–43.

34. Taylor FGM, Quirke P, Heald RJ, Moran B, Blomqvist L, Swift I, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. Ann Surg. 2011 Apr;253(4):711–9.

35. Elmashad NM, Hamisa MF, Hazem Ziada D, Fatah ONA, Arafat W. Role of MRI in rectal carcinoma after chemo irradiation therapy with pathological correlation. Alex J Med [Internet]. [cited 2015 Nov 8]; Available from: http://www.sciencedirect.com/science/article/pii/S2090506814001110

36. Patel UB, Taylor F, Blomqvist L, George C, Evans H, Tekkis P, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. J Clin Oncol Off J Am Soc Clin Oncol. 2011 Oct 1;29(28):3753–60.

37. Mandard A-M, Dalibard F, Mandard J-C, Marnay J, Henry-Amar M, Petiot J-F, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer. 1994 Jun 1;73(11):2680–6.

38. Benson AB, Venook AP, Bekaii-Saab T, Chan E, Chen Y-J, Cooper HS, et al. Rectal Cancer, Version 2.2015. J Natl Compr Cancer Netw JNCCN. 2015 Jun;13(6):719–728; quiz 728.

39. Blomqvist L, Glimelius B. The “good”, the “bad”, and the “ugly” rectal cancers. Acta Oncol Stockh Swed. 2008;47(1):5–8.

40. Glynne-Jones R, Tan D, Goh V. Pelvic MRI for guiding treatment decisions in rectal cancer. Oncol Williston Park N. 2014 Aug;28(8):667–77.

41. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006 Oct;93(10):1215–23.

42. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman

Radiation Oncology Group trial 01.04. J Clin Oncol Off J Am Soc Clin Oncol. 2012 Nov 1;30(31):3827–33.

43. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. J Clin Oncol [Internet]. [cited 2016 Jun 25]; Available from: http://meetinglibrary.asco.org/content/76910-102

44. Gérard J-P, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne P-L, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol Off J Am Soc Clin Oncol. 2010 Apr 1;28(10):1638–44.

45. WILLETT CG, DUDA DG, CZITO BG, BENDELL JC, CLARK JW, JAIN RK. Targeted Therapy in Rectal Cancer. Oncol Williston Park N. 2007 Aug;21(9):1055–passim.

46. Habr-Gama A, Perez R, Proscurshim I, Gama-Rodrigues J. Complete clinical response after neoadjuvant chemoradiation for distal rectal cancer. Surg Oncol Clin N Am. 2010 Oct;19(4):829–45.

47. Brodsky JT, Richard GK, Cohen AM, Minsky BD. Variables correlated with the risk of lymph node metastasis in early rectal cancer. Cancer. 1992 Jan 15;69(2):322–6.

48. You YN. Local excision: is it an adequate substitute for radical resection in T1/T2 patients? Semin Radiat Oncol. 2011 Jul;21(3):178–84.

49. Minsky BD, Rich T, Recht A, Harvey W, Mies C. Selection criteria for local excision with or without adjuvant radiation therapy for rectal cancer. Cancer. 1989 Apr 1;63(7):1421–9.

50. Nakagoe T, Ishikawa H, Sawai T, Tsuji T, Tanaka K, Hidaka S, et al. Survival and recurrence after a sphincter-saving resection and abdominoperineal resection for adenocarcinoma of the rectum at or below the peritoneal reflection: a multivariate analysis. Surg Today. 2004;34(1):32–9.

51. The Long-term Oncological Outcome of a Sphincter-saving Resection and an Abdominoperineal Resection for Lower Rectal Cancer [Internet]. [cited 2016 Aug 14]. Available from: http://synapse.koreamed.org/DOIx.php?id=10.3393/jksc.2007.23.3.186&vmode=PUBREADER

52. Ortiz H, Armendariz P. Anterior resection: do the patients perceive any clinical benefit? Int J Colorectal Dis. 1996;11(4):191–5.

53. Rothenberger DA, Wong WD. Abdominoperineal resection for adenocarcinoma of the low rectum. World J Surg. 1992 Jun;16(3):478–85.

54. McLeod RS. Comparison of Quality of Life in Patients Undergoing Abdominoperineal Extirpation or Anterior Resection for Rectal Cancer. Ann Surg. 2001 Feb;233(2):157–8.

55. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg. 1982 Oct;69(10):613–6.

56. Damin DC, Lazzaron AR. Evolving treatment strategies for colorectal cancer: A critical review of current therapeutic options. World J Gastroenterol WJG. 2014 Jan 28;20(4):877–87.

57. Bruch HP, Schwandner O, Schiedeck TH, Roblick UJ. Actual standards and controversies on operative technique and lymph-node dissection in colorectal cancer. Langenbecks Arch Surg Dtsch Ges Für Chir. 1999 Apr;384(2):167–75.

58. Bianchi PP, Petz W, Luca F, Biffi R, Spinoglio G, Montorsi M. Laparoscopic and robotic total mesorectal excision in the treatment of rectal cancer. Brief review and personal remarks. Front Oncol. 2014;4:98.

59. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet Lond Engl. 2001 Oct 20;358(9290):1291–304.

60. Wolmark N, Wieand HS, Hyams DM, Colangelo L, Dimitrov NV, Romond EH, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. J Natl Cancer Inst. 2000 Mar 1;92(5):388–96.

61. Thomas PRM, Lindblad AS. Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: A review of the gastrointestinal tumor study group experience. Radiother Oncol. 1988 Dec 1;13(4):245–52.

62. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med. 1991 Mar 14;324(11):709–15.

63. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: Long Lasting Benefits From Radiotherapy on Survival and Local Recurrence Rate. J Clin Oncol. 2005 Aug 20;23(24):5644–50.

64. Francois Y, Nemoz CJ, Baulieux J, Vignal J, Grandjean JP, Partensky C, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol Off J Am Soc Clin Oncol. 1999 Aug;17(8):2396.

65. Marijnen C a. M, Kapiteijn E, van de Velde CJH, Martijn H, Steup WH, Wiggers T, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol Off J Am Soc Clin Oncol. 2002 Feb 1;20(3):817–25.

66. Bosset J-F, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with Preoperative Radiotherapy in Rectal Cancer. N Engl J Med. 2006 Sep 14;355(11):1114–23.

67. Bosset J-F, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun R-J, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol. 2014 Feb;15(2):184–90.

68. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet Lond Engl. 2009 Mar 7;373(9666):811–20.

69. Hofheinz R-D, Wenz F, Post S, Matzdorff A, Laechelt S, Hartmann JT, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol. 2012 Jun;13(6):579–88.

70. Aldridge MC, Phillips RK, Hittinger R, Fry JS, Fielding LP. Influence of tumour site on presentation, management and subsequent outcome in large bowel cancer. Br J Surg. 1986 Aug;73(8):663–70.

71. Clinico-pathological features of prognostic significance in operable rectal cancer in 17 centres in the U.K. (Third report of the M.R.C. Trial, on behalf of the Working Party) [Internet]. [cited 2016 Aug 14]. Available from: http://images.biomedsearch.com/6487514/brjcancer00108-

0005.pdf?AWSAccessKeyId=AKIAIBOKHYOLP4MBMRGQ&Expires=1471305600&Signature=hXm3mi9ixoKj8XTLsmyfMMDqB8I%3D

72. Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P. The prognostic inhomogeneity in pT3 rectal carcinomas. Int J Colorectal Dis. 2001 Sep;16(5):298–304.

73. Dukes CE. The classification of cancer of the rectum. J Pathol Bacteriol. 1932 Jan 1;35(3):323–32.

74. Hermanek P, Merkel S, Fietkau R, Rödel C, Hohenberger W. Regional lymph node metastasis and locoregional recurrence of rectal carcinoma in the era of TNM surgery. Implications for treatment decisions. Int J Colorectal Dis. 2009 Dec 10;25(3):359–68.

75. Hall MNR, Finan PJ, Al-Jaberi T, Tsang CS, Brown SR, Dixon MF, et al. Circumferential margin involvement after mesorectal excision of rectal cancer with curative intent. Dis Colon Rectum. 1998 Aug;41(8):979–83.

76. Sasaki O, Atkin WS, Jass JR. Mucinous carcinoma of the rectum. Histopathology. 1987 Mar;11(3):259–72.

77. Chapuis PH, Dent OF, Fisher R, Newland RC, Pheils MT, Smyth E, Colquhoun KA multivariate analysis of clinical and pathological variables in prognosis after resection of large bowel cancer. Br J Surg 72: 698-702 [Internet]. [cited 2016 Aug 14]. Available from: https://www.researchgate.net/publication/19119673_Chapuis_PH_Dent_OF_Fisher_R_Newland_RC_Pheils_MT_Smyth_E_Colquhoun_KA_multivariate_analysis_of_clinical_and_pathological_variables_in_prognosis_after_resection_of_large_bowel_cancer_Br_J_Surg_72_698-7

78. Gunderson LL, Martenson JA, Smalley SR, Garton GR. Lower gastrointestinal cancers: rationale, results, and techniques of treatment. Front Radiat Ther Oncol. 1994;28:140–54.

79. Mohiuddin M, Regine WF, Marks G. Prognostic significance of tumor fixation of rectal carcinoma. Implications for adjunctive radiation therapy. Cancer. 1996 Aug 15;78(4):717–22.

80. Habib NA, Peck MA, Sawyer CN, Blaxland JW, Luck RJ. Does fixity affect prognosis in colorectal tumours? Br J Surg. 1983 Jul 1;70(7):423–4.

81. Fokas E, Liersch T, Fietkau R, Hohenberger W, Beissbarth T, Hess C, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. J Clin Oncol Off J Am Soc Clin Oncol. 2014 May 20;32(15):1554–62.

82. MacGregor TP, Maughan TS, Sharma RA. Pathological grading of regression following neoadjuvant chemoradiation therapy: the clinical need is now. J Clin Pathol. 2012 Oct;65(10):867–71.

83. Ryan R, Gibbons D, Hyland JMP, Treanor D, White A, Mulcahy HE, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology. 2005 Aug;47(2):141–6.

84. Rödel C, Martus P, Papadoupolos T, Füzesi L, Klimpfinger M, Fietkau R, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2005 Dec 1;23(34):8688–96.

85. Laufman H, Saphir O. Primary linitis plastica type of carcinoma of the colon. AMA Arch Surg. 1951 Jan;62(1):79–91.

86. Hyngstrom JR, Hu C-Y, Xing Y, You YN, Feig BW, Skibber JM, et al. Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: analysis from the National Cancer Data Base. Ann Surg Oncol. 2012 Sep;19(9):2814–21.

87. Hamilton SR, Vogelstein B, Kudo S, et al. Carcinoma ofthe colon and rectum In: Hamilton SR, Aaltonen LA (eds). Pathology and Genetics of Tumors of the Digestive System. IARC Press: Lyon, 2000.

88. Pande R, Sunga A, Levea C, Wilding GE, Bshara W, Reid M, et al. Significance of signet-ring cells in patients with colorectal cancer. Dis Colon Rectum. 2008 Jan;51(1):50–5.

89. Tung SY, Wu CS, Chen PC. Primary signet ring cell carcinoma of colorectum: an age- and sex-matched controlled study. Am J Gastroenterol. 1996 Oct;91(10):2195–9.

90. Kang H, O'Connell JB, Maggard MA, Sack J, Ko CY. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum. 2005 Jun;48(6):1161–8.

91. Fu K-I, Sano Y, Kato S, Saito H, Ochiai A, Fujimori T, et al. Primary signet-ring cell carcinoma of the colon at early stage: a case report and a review of the literature. World J Gastroenterol. 2006 Jun 7;12(21):3446–9.

92. Chen J-S, Hsieh P-S, Chiang J-M, Yeh C-Y, Tsai W-S, Tang R, et al. Clinical outcome of signet ring cell carcinoma and mucinous adenocarcinoma of the colon. Chang Gung Med J. 2010 Feb;33(1):51–7.

93. Bonello JC, Quan SH, Sternberg SS. Primary linitis plastica of the rectum. Dis Colon Rectum. 1980 Aug;23(5):337–342U.

94. King-Yin Lam A, Ong K, Ho Y-H. Colorectal mucinous adenocarcinoma: the clinicopathologic features and significance of p16 and p53 expression. Dis Colon Rectum. 2006 Sep;49(9):1275–83.

95. Gopalan V, Smith RA, Ho Y-H, Lam AK-Y. Signet-ring cell carcinoma of colorectum--current perspectives and molecular biology. Int J Colorectal Dis. 2011 Feb;26(2):127–33.

96. Jayanand SB, Seshadri RA, Tapkire R. Signet ring cell histology and non-circumferential tumors predict pathological complete response following neoadjuvant chemoradiation in rectal cancers. Int J Colorectal Dis. 2011 Jan;26(1):23–7.

97. Anthony T, George R, Rodriguez-Bigas M, Petrelli NJ. Primary signet-ring cell carcinoma of the colon and rectum. Ann Surg Oncol. 1996 Jul;3(4):344–8.

98. Ooi BS, Ho YH, Eu KW, Seow Choen F. Primary colorectal signet-ring cell carcinoma in Singapore. ANZ J Surg. 2001 Dec;71(12):703–6.

99. Messerini L, Palomba A, Zampi G. Primary signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum. 1995 Nov;38(11):1189–92.

100. Makino T, Tsujinaka T, Mishima H, Ikenaga M, Sawamura T, Nakamori S, et al. Primary signet-ring cell carcinoma of the colon and rectum: report of eight cases and review of 154 Japanese cases. Hepatogastroenterology. 2006 Dec;53(72):845–9.

101. Bratland A, Vetrhus T, Grøholt KK, Ree AH. Preoperative radiotherapy in rectal signet-ring cell carcinoma - magnetic resonance imaging and treatment outcome: Report of six cases. Acta Oncol Stockh Swed. 2010;49(1):42–9.

102. Engineer R, Basu T, Chopra S, Arya S, Patil P, Mehta S, et al. Factors influencing response to neoadjuvant chemoradiation and outcomes in rectal cancer patients: tertiary Indian cancer hospital experience. J Gastrointest Oncol. 2015 Apr;6(2):155–64.

103. Kang H, O'Connell JB, Maggard MA, Sack J, Ko CY. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum. 2005;48(6):1161–1168.

104. Bittorf B, Merkel S, Matzel KE, Wein A, Dimmler A, Hohenberger W. Primary signet-ring cell carcinoma of the colorectum. Langenbecks Arch Surg Dtsch Ges Für Chir. 2004 Jun;389(3):178–83.

105. Shiloh Y. The ATM-mediated DNA-damage response: taking shape. Trends Biochem Sci. 2006 Jul;31(7):402–10.

106. D'Amours D, Jackson SP. The Mre11 complex: at the crossroads of dna repair and checkpoint signalling. Nat Rev Mol Cell Biol. 2002 May;3(5):317–27.

107. Durocher D, Jackson SP. DNA-PK, ATM and ATR as sensors of DNA damage: variations on a theme? Curr Opin Cell Biol. 2001 Apr;13(2):225–31.

108. Löbrich M, Jeggo PA. The impact of a negligent G2/M checkpoint on genomic instability and cancer induction. Nat Rev Cancer. 2007 Nov;7(11):861–9.

109. van Gent DC, van der Burg M. Non-homologous end-joining, a sticky affair. Oncogene. 2007 Dec 10;26(56):7731–40.

110. Kunkel TA, Erie DA. DNA mismatch repair. Annu Rev Biochem. 2005;74:681–710.

111. de la Chapelle A. Microsatellite instability. N Engl J Med. 2003 Jul 17;349(3):209–10.

112. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Rüschoff J, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004 Feb 18;96(4):261–8.

113. Haydon AMM, Jass JR. Emerging pathways in colorectal-cancer development. Lancet Oncol. 2002 Feb;3(2):83–8.

114. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol Off J Am Soc Clin Oncol. 2005 Jan 20;23(3):609–18.

115. Umar A, Risinger JI, Hawk ET, Barrett JC. Testing guidelines for hereditary non-polyposis colorectal cancer. Nat Rev Cancer. 2004 Feb;4(2):153–8.

116. Vasen HFA, Möslein G, Alonso A, Bernstein I, Bertario L, Blanco I, et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet. 2007 Jun;44(6):353–62.

117. Shin J-S, Tut TG, Yang T, Lee CS. Radiotherapy Response in Microsatellite Instability Related Rectal Cancer. Korean J Pathol. 2013 Feb;47(1):1–8.

118. Kakar S, Smyrk TC. Signet ring cell carcinoma of the colorectum: correlations between microsatellite instability, clinicopathologic features and survival. Mod Pathol Off J U S Can Acad Pathol Inc. 2005 Feb;18(2):244–9.

119. Kim IY. Impact of Microsatellite Instability in Signet-Ring Cell and Mucinous Components in Patients With Colorectal Carcinoma. Ann Coloproctology. 2016 Apr;32(2):45–6.

120. Cottet V, Bouvier V, Rollot F, Jooste V, Bedenne L, Faivre J, et al. Incidence and patterns of late recurrences in rectal cancer patients. Ann Surg Oncol. 2015 Feb;22(2):520–7.

121. Garofalo M, Moughan J, Hong T, Bendell J, Berger A, Lerma F, et al. RTOG 0822: A Phase II Study of Preoperative (PREOP) Chemoradiotherapy (CRT) Utilizing IMRT in Combination with Capecitabine (C) and Oxaliplatin (O) for Patients with Locally Advanced Rectal Cancer. Int J Radiat Oncol • Biol • Phys. 2011 Oct 1;81(2):S3–

4.

122**.** Best MRI predictors of complete response to neoadjuvant chemo radiation in locally advanced rectal cancer Sathyakumar K, Chandramohan A, Masih D, Jesudasan MR, Pulimood A, Eapen A Br J Radiol. 2016;89(1060):20150328. doi: 10.1259/bjr.20150328. Epub 2016 Feb 1**.**

9. APPENDIX

INFORMATION SHEET

Christian Medical College, Vellore

Department of Radiation therapy

MRI DOWNSTAGING, PATHOLOGICAL RESPONSE AND MICROSATELLITE INSTABILITY STATUS IN PATIENT'S WITH SIGNET RING CELL CARCINOMA RECTUM UNDERGOING PREOPERATIVE LONG COURSE CHEMO IRRADIATION

You are being requested to participate in a study which will assess the response of your tumor to radiation therapy and see the relationship between MSI status and radiation response.

You will be undergoing treatment of your condition as per current standard practice. MRI pelvis will be done during initial evaluation and after 6 weeks of radiation therapy. The Radiologist will compare the stage between the pre and post radiation therapy MRI. If the tumor is operable as per opinion of Colorectal Surgeons and the MRI findings you will undergo the appropriate surgery

Our Pathologist will report the pathological response to radiation therapy in the surgical specimen. A special test called immunohistochemistry will be done on your diagnostic biopsy specimen to test MSI status.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to

withdraw permission to participate in this study. If you do so, this will not affect your treatment at this hospital in any way.

What will happen if you develop any study related injury?

We do not expect any injury to occur.

Will you have to pay for the test?

You will have to pay for MRI and treatment as it is considered the standard of care .As we are investigating the role of MSI in radiation response, you will not have to pay for MSI immunohistochemistry.

Will my treatment details be kept confidential?

All your treatment details will not be revealed to any third party The results will be reviewed only by people associated with the study.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask

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MRI DOWNSTAGING, PATHOLOGICAL RESPONSE AND MICROSATELLITE INSTABILITY STATUS IN PATIENT'S WITH SIGNET RING CELL CARCINOMA RECTUMUNDERGOING PREOPERATIVE LONG COURSE CHEMO IRRADIATION

INFORMED CONSENT

Sl. Number:

Participant ID: Date:

Participant name: Hospital Number:

I Mr / Mrs ……, Son/Daughter

of…….. Hospital number …… have been

explained in a language that I clearly understand about the nature of the condition and its associated prognosis. The options, the benefits of the proposed line of standard treatment and the side effects have been clearly explained to me. The costs associated with treatment have also been mentioned.

I have understood that my clinical,radiological and pathological information will be used for research purpose. The aim, the methods of collection and usage of the data, the proposed end points have been clearly explained to me by Dr. Rajkrishna B

I am aware that the data collected from my participation in this study, will be utilized for correlating radiotherapy response.

I am aware that my participation in this study is entirely voluntary.

I am also aware that I may, at any time of the study, seek more information regarding the

same. I may wish to withdraw from the study at any point, after suitable intimation, for reasons that I may not be willing to share.

I hereby give my informed consent for participation in the study. My consent has been given under my own free will and under no undue or external coercion.

PARTICIPANT	WITNESS
NAME IN CAPITALS:	NAME IN CAPITALS:
SIGNATURE:	SIGNATURE:
THUMB IMPRESSION:	THUMB IMPRESSION:
PLACE:	PLACE:
ADDRESS	ADDRESS
CONTACT NUMBER:	CONTACT NUMBER:
DATE AND TIME:	DATE AND TIME:

INVESTIGATOR'S NAME AND SIGNATURE

DATE

No	Age	SEX	Marital sta	OCCUPAT	NATIONA	ECOG	Distance f	Pretreatm	Diversion	BIOPSY	MSI	MLH1	MSH6	MSH2	PRE RT ST	T STAGE	N STAGE
1	62	MALE	MARRIED	SKILLED	NON INDI	1	4	26.2	YES	SIGNET + I	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T3bN1	T3	N1
2	48	FEMALE	MARRIED	UNSKILLE	INDIAN	1	0	2.57	YES	SIGNET + I	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T3bN1	T3	N1
3	32	MALE	MARRIED	UNSKILLE	INDIAN	1	0.5	4.53	YES	SIGNET + I	NOT ASSE	.	.	.	T3bN2	T3	N2
4	44	MALE	MARRIED	SKILLED	INDIAN	1	5	5.87	YES	SIGNET RI	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T4aN2	T4	N2
5	57	MALE	MARRIED	SKILLED	INDIAN	1	6	8.43	NO	SIGNET + I	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T2N1	T2	N1
6	33	FEMALE	MARRIED	UNSKILLE	NON INDI	1	8	4.94	YES	SIGNET RI	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T4aN2	T4	N2
7	62	MALE	MARRIED	UNSKILLE	INDIAN	1	7	2.78	NO	SIGNET RI	NOT ASSE	.	.	.	T4aN1	T4	N1
8	22	FEMALE	MARRIED	UNSKILLE	NON INDI	1	3	2.04	NO	SIGNET RI	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T3dN2	T3	N2
9	23	FEMALE	MARRIED	UNSKILLE	INDIAN	1	5	2.17	NO	SIGNET + I	NOT ASSE	.	.	.	T3N2	T3	N2
10	46	MALE	MARRIED	UNSKILLE	INDIAN	1	7	2.79	NO	SIGNET + I	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T3N2	T3	N2
11	38	FEMALE	MARRIED	SKILLED	INDIAN	1	5	0.797	NO	SIGNET RI	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T3cN2	T3	N2
12	39	FEMALE	MARRIED	SKILLED	INDIAN	1	3	18.1	NO	SIGNET + I	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T3cN2	T3	N2
13	26	FEMALE	MARRIED	UNSKILLE	INDIAN	1	8	0.57	NO	SIGNET RI	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T3cN2	T3	N2
14	26	MALE	UNMARRI	UNSKILLE	NON INDI	1	1	4.49	YES	SIGNET + I	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T2N1	T2	N1
15	37	MALE	MARRIED	UNSKILLE	INDIAN	1	3	28.7	NO	SIGNET RI	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T3N1	T3	N1
16	60	MALE	MARRIED	UNSKILLE	INDIAN	1	1	4.39	NO	SIGNET RI	NOT ASSE	.	.	.	T3N0	T3	N0
17	43	MALE	MARRIED	UNSKILLE	INDIAN	1	0	1.14	YES	SIGNET + I	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T3cN1	T3	N1
18	27	MALE	MARRIED	UNSKILLE	INDIAN	1	3	10.8	NO	SIGNET RI	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T3N2	T3	N2
19	18	MALE	UNMARRI	UNSKILLE	INDIAN	1	1	5.74	YES	SIGNET RI	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T3N2	T3	N2
20	30	MALE	MARRIED	UNSKILLE	NON INDI	1	4	6.92	YES	SIGNET RI	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T3N2	T3	N2
21	25	FEMALE	MARRIED	UNSKILLE	INDIAN	1	6	250	NO	SIGNET + I	NOT ASSE	.	.	.	T3N2	T3	N2
22	32	FEMALE	MARRIED	UNSKILLE	INDIAN	1	3	3.51	NO	SIGNET RI	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	T4aN2	T4	N2

CRM	RT DOSE	FRACTION	CAPECITA	RT TECHNI	TRG MRI	POST RT C	SURGERY	PATHOLO	ypN	ypT	PATHOLOGICAL TRG		POST OP	MARGIN	
INVOLVED	5040	25	NO	IMRT	absence o	608	INOPERAE	.	.	.	.		.		
INVOLVED	5040	28	YES	2D	.	2.71	INOPERAE	.	.	.	.		.		
INVOLVED	5040	28	YES	2D	absence o	2.74	INOPERAE	.	.	.	.		.		
INVOLVED	5040	28	YES	2D	residual ca	3.04	INOPERAE	.	.	.	.		.		
UNINVOLV	5040	28	YES	IMRT	residual ca	5.22	AR	T2N0	N0	T2	NEAR COMPLETE RES		NEGATIVE		
INVOLVED	5040	28	YES	2D	residual ca	3.11	EXENTERA	T3N1b	N1	T3	MINIMAL RESPONSE		NEGATIVE		
INVOLVED	5040	28	YES	2D	residual ca	1.78	HARTMAN	T3N0	N0	T3	NO RESPONSE		NEGATIVE		
INVOLVED	5040	28	YES	2D	residual ca	1.36	APE	T3N0	N0	T3	NO RESPONSE		NEGATIVE		
INVOLVED	5040	28	YES	2D	residual ca	1.9	AR	T0N0	N0	T0	COMPLETE RESPONS		NEGATIVE		
INVOLVED	5040	28	YES	3D	predomin	2.58	AR	T0N0	N0	T0	COMPLETE RESPONS		NEGATIVE		
INVOLVED	5040	28	YES	3D	residual ca	0.74	AR	T3N0	N0	T3	NEAR COMPLETE RES		NEGATIVE		
INVOLVED	5040	28	YES	2D	residual ca	4.59	APE	T2N0	N0	T2	NEAR COMPLETE RES		NEGATIVE		
INVOLVED	5040	28	YES	2D	residual ca	1.2	AR	T0N0	N0	T0	COMPLETE RESPONS		NEGATIVE		
INVOLVED	5040	28	YES	2D	absence o	3.99	APE	T0N0	N0	T0	COMPLETE RESPONS		NEGATIVE		
INVOLVED	5040	28	YES	2D	predomin	9.28	APE	T4aN2a	N2	T4	NO RESPONSE		POSITIVE		
THREATEN	5040	28	YES	2D	rare resid	1.81	APE	T1N0	N0	T1	NEAR COMPLETE RES		NEGATIVE		
INVOLVED	5040	28	YES	2D	absence o	1.83	INOPERAE	.	.	.	.		.		
INVOLVED	5040	28	YES	2D	residual ca	3.71	APE	T0N0	N0	T0	COMPLETE RESPONS		NEGATIVE		
INVOLVED	5040	28	YES	2D	residual ca	3.2	INOPERAE	.	.	.	.		.		
INVOLVED	5040	28	YES	2D	predomin	19.1	INOPERAE	.	.	.	.		.		
.	5040	28	YES	2D	residual ca	11.6	HARTMAN	T3N2a	N2	T3	NO RESPONSE		NEGATIVE		
INVOLVED	5040	28	YES	3D	absence o	1.15	APE	T0N0	N0	T0	COMPLETE RESPONS		NEGATIVE		